OBSTETRICS

Vaginal progesterone combined with cervical pessary: A chance for pregnancies at risk for preterm birth?

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BACKGROUND: Precocious cervical ripening, as defined by cervical shortening on transvaginal sonography, has prompted a broad evaluation of secondary strategies (such as cerclage, vaginal progesterone, or a cervical pessary) to prevent preterm delivery. However, there is still a lack of direct comparisons between individual treatments or their combinations.

OBJECTIVE: We sought to compare at-risk patients and screening patients who had been treated with cervical pessary alone with patients who had been treated with pessary plus vaginal progesterone.

STUDY DESIGN: This is a pre- and postintervention cohort study from a preterm labor clinic where placement of a cervical pessary has been the standard treatment since 2008 for at-risk women defined by (1) a history of spontaneous preterm birth at <37 weeks of gestation, (2) conization, or (3) a cerclage because of a previous short cervical length of <3rd percentile and, additionally, with a cervical length of <10th percentile in the ongoing pregnancy. Patients who did not meet the criteria for the "at risk" group, but who had a cervical length of <3rd percentile comprised the screening group. From July 2011 onward, vaginal progesterone (200 mg, suppositories) was prescribed in addition to the pessary. Both at-risk patients (n = 55) and screening patients (n = 51) were treated at the time of diagnosis. The primary outcome was the rate of preterm deliveries at <34 weeks of gestation. Secondary outcomes included deliveries at <28, <32, and <37 weeks of gestation, the days from start of therapy until delivery, a composite index of neonatal outcome, and the number of days in the neonatal intensive care unit. Primary and secondary outcomes were compared between groups with the use of multivariable models to adjust for possible confounders.

RESULTS: Delivery at <34 weeks of gestation occurred in 17 of 53 patients (32.1%) who were treated with pessary plus progesterone, compared with 13 of 53 patients (24.5%) who were treated with pessary alone ($P = .57$). Similarly, there was no difference in the rate of preterm delivery at <28, <32, or <37 weeks of gestation. The composite poor neonatal outcome was 15.1% in the pessary group vs 18.9% in the combined group ($P = .96$). The mean duration of stay in the neonatal intensive care unit was 46.5 days (range, 9-130 days) in the combined vs 52.0 days (range, 3-151 days) in the pessary group ($P < .001$).

CONCLUSION: In this cohort study, treatment of precocious cervical ripening with cervical pessary plus vaginal progesterone did not reduce the rates of preterm delivery at <28, <32, <34, or <37 weeks of gestation compared with pessary alone. The neonatal intensive care use was shorter in patients who received additional vaginal progesterone, although there was no difference in composite poor neonatal outcome. These preliminary results may serve as a pilot for future trials and provide a basis for treatment until larger trials are completed.

Key words: cerclage, cervical pessary, precocious cervical ripening, prematurity, preterm delivery, preterm birth, short cervix, transvaginal sonography, vaginal progesterone

Preterm birth (PTB) is the major cause of perinatal morbidity and death in high resourced countries, with a prevalence of 5.3% (Latvia) up to 12% (United States).[1,2] Primary prevention rarely has been shown to be effective apart from a few studies that sought to reduce either physical stress by public health interventions[3] or smoking by smoke-free legislation.[4] After the introduction of transvaginal sonography (TVS) as a tool to identify and follow women who are at risk for PTB,[5,6] secondary preventive concepts such as progesterone[7] or a cervical pessary[8] were reintroduced as a treatment for women with precocious cervical ripening.[9-12] In addition, the indication for a cerclage was reevaluated on the basis of TVS results.[13]

In our preterm labor clinic, we have placed cervical pessaries in singleton pregnancies with a short cervix since October 2008. Starting in July 2011, we added the administration of vaginal progesterone based on the publication of Hassan et al[10] hoping that the 2 approaches might provide complementary secondary preventive effects in high-risk pregnancies and pregnancies that, with screening, had a short cervical length (CL). The aims of this study were to develop intermediate information for patients whose treatment cannot await the results of large randomized controlled trials (RCTs) and to serve as a pilot for planning future trials.[14-17]

Materials and Methods

A pre- and postintervention cohort study was conducted from October 2008 to December 2014 in women with singleton pregnancies at increased risk for PTB by both history and cervical shortening and a screening group without risks but who were found to have isolated cervical shortening. Within this period, 13,179 examinations were performed in 4393 patients who had been referred to our outpatient unit for various reasons that included increased risk factors for PTB. The risk group of this study population was characterized by a history of PTB at <37 weeks of gestation (n = 35), of whom 26 of 35 patients (74.3%) had a previous PTB at <32 weeks of gestation, a history of

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surgical conization (n = 18), a cerclage because of a previous short CL at <3rd percentile (n = 11) or a combination of cerclage and previous conization (n = 2; Table 1). In total, 6 patients in the pessary group and 5 patients in the combined group had both a previous PTB and a conization or cerclage, and they were considered for calculations in both categories. Patients who did not meet criteria for the "at-risk" group, but who had a CL at <3rd percentile, comprised the screening group that was detected during the second-trimester screening scan at our ultrasound unit. The gestational age of referral ranged between 12 and 27 + 1 weeks in the risk group and 17 + 1 and 27 + 6 weeks in the screening group. A perforated Arabin cerclage pessary (Dr Arabin GmbH & Co KG, Witten, Germany) was applied. The sizes were chosen according to previously published recommendations related to height and upper and lower diameters.[18] In our study population with only singleton pregnancies, the height was always 21 mm, and the upper diameter was 32 mm, except for patients with severe funneling for whom an upper diameter of 35 mm is recommended. Dependent on the obstetric history the lower diameter was 65 mm in women without and 70 mm in women with a previous vaginal delivery. The device is CE (Conformité Européenne) approved for the prevention of preterm labor (MEDCERT 0482, certificate 10610 GB 412, 150 324). The pessary was placed when the CL was <10th percentile[19] (eg, 34.9, 29.2, and 25.2 mm at 16, 24, and 28 weeks of gestation, respectively) in the risk group and when the CL was <3rd percentile[19] (eg, 30.5, 23.4, and 18.7 mm at 16, 24, and 28 weeks of gestation, respectively) in screening patients (Table 1). Only patients with a start of treatment at ≥12 and <28 weeks of gestation were included for further analysis. For the interval of 12-16 weeks of gestation, we extrapolated the Salomon percentiles by using the percentiles of Gramellini et al[20] (32.8 mm for the 3rd percentile and 37.5 mm for the 10th percentile at 12 weeks of gestation). The success of pessary treatment depends on both standardized cervical sonography and the skills of the obstetrician in charge because there is a well-defined learning curve.[21] Therefore, patients were included only if they had been diagnosed and treated by 1 experienced specialist who also followed all high-risk referrals of this study. All patients had been examined by TVS according to the Fetal Medicine Foundation in the first trimester[22] and by the method described by Iams et al[6] from 16 weeks of gestation onwards that was redefined by To et al.[23] Funneling was classified as a V-, Y- or U-shaped dilation of the internal os with at least a width of 5 mm.[24]

Patients and involved specialists were informed about pessary insertion and possible side-effects (such as vaginal discharge), and the treatment followed a prescribed protocol.[24] During the insertion, the pessary was squeezed, introduced longitudinally, and unfolded only in the upper fornix whereby the smaller inner ring was directed towards the cervix. The proximal part of the pessary's dome was pushed carefully until the cervix was surrounded; the anterior part of the pessary was then pressed slightly towards the sacrum.[18] The pessary remained until 37 weeks of gestation, premature preterm rupture of membranes (PPROM), or regular contractions that suggested active labor. In 1 patient, the pessary was removed because of mechanical irritation, and a smaller version was inserted. Patients who complained about discharge were reassured that this should not be confused with infection or PPROM. Patients were seen 1 week after pessary insertion, at which time a TVS was performed by placing the transducer on top of the anterior cervix, thus avoiding shadowing by the pessary and cervical manipulation. Thereafter, screening patients were followed by their own gynecologist if there were no further problems. High-risk pregnancies with previous PTB, perinatal losses, or radical conization were followed within our outpatient unit until at least 32 weeks of gestation.

From July 2011 onward, informed consent included information on recent studies of vaginal progesterone that was administered as 200-mg vaginal suppositories in the evening; thereafter, patients received combined therapy. In total, 53 patients received a "pessary only," and 53 patients received both pessary and vaginal progesterone (Table 1). For the whole study, we calculated a comparability score[25] of 11 of 12 points, 1 point for midyear interval (eg, the time interval between different policies) and 2 points for each other variable (geographic setting, health care setting, health care providers, confounding interventions impact, consensus statements impact).

Exclusion criteria were major fetal abnormalities, PPROM before the start of therapy, ballooning membranes (beyond the external os), vaginal bleeding, and painful or regular contractions before the start of therapy.

The primary outcome was the rate of PTB at <34 weeks of gestation. Preterm cesarean delivery at <37 weeks of gestation was indicated because of severe preeclampsia (n = 1), suspected chorioangioma (n = 1), placenta previa (n = 1), suspicious fetal heart rate monitoring without regular contractions (n = 1), PPROM (n = 12), chorioamnionitis (n = 3), regular contractions with >5 cm dilation combined with abnormal presentation (n = 3), pathologic fetal heart rate pattern (n = 6), or prolonged labor (n = 1). Secondary outcomes included rates of PTB at <28, <32, and <37 completed weeks of gestation, birth weight, admission to the neonatal intensive care unit (NICU), the number of days in the NICU, the composite poor neonatal outcome defined by perinatal or neonatal death, respiratory distress syndrome more than grade II, bronchopulmonary dysplasia, intraventricular hemorrhage grade III or IV, and necrotizing enterocolitis. Days of neonatal hospitalization were analyzed separately. All data were retrieved from our hospital data system and double checked with paper charts. Statistical analyses were performed with *R* (version 3.1.1 for Windows) with the use of the packages survival, political science computational laboratory, and Microsoft Office Excel 2007 (Microsoft Corporation, Redmond, WA).

Baseline characteristics were analyzed with the use of *t*-tests and χ^2-tests.

TABLE 1
Baseline characteristics of the study population

Variable	Risk group[a]			Screening group[b]			Total population[c]		
	Pessary (n = 27)	Pessary and progesterone (n = 28)	*P* value	Pessary (n = 26)	Pessary and progesterone (n = 25)	*P* value	Pessary (n = 53)	Pessary and progesterone (n = 53)	*P* value
Age, y[d]	31.4 ± 6.13	32.7 ± 3.68	.347	30.3 ± 6.74	31.7 ± 5.14	.408	30.9 ± 6.40	32.2 ± 4.41	.203
Body mass index, kg/m^2[d]	23.3 ± 3.67	22.8 ± 4.76	.657	24.0 ± 3.77	23.6 ± 3.29	.634	23.7 ± 3.70	23.2 ± 4.11	.506
Smoker, n (%)	3 (11.1)	2 (7.1)	.669	2 (7.7)	2 (8.0)	1	5 (9.4)	4 (7.5)	1
Obstetric history, n (%)[e]									
Nulliparous	4 (14.8)	4 (14.3)	1	14 (53.8)	18 (72.0)	.293	18 (34.0)	22 (41.5)	.548
Obstetric history of preterm birth									
≤32 Weeks of gestation	14 (51.9)	12 (42.9)	.671	—	—	—	14 (26.4)	12 (22.6)	.822
32-37 Weeks of gestation	5 (18.5)	4 (14.3)	.671	—	—	—	5 (9.4)	4 (7.6)	.822
History of surgical conization or treatment for threatening preterm birth with a cervical length of <3rd percentile by a cerclage, n (%)									
Cervical cerclage	5 (18.5)	6 (21.4)	.665	—	—	—	5 (9.4)	6 (11.3)	.689
Surgical conization	9 (33.3)	9 (32.1)	.665	—	—	—	9 (17.0)	9 (17)	.689
Both, conization and cerclage	0	2 (7.14)	.665	—	—	—	0	2 (3.8)	.689
Course of pregnancy									
Median gestational age at start of therapy, wk + d (range)	19 + 3 (12 + 0–27 + 1)	19 + 0 (12 + 0–26 + 4)	.707	24 + 0 (17 + 1–27 + 6)	23 + 6 (17 + 1–27 + 6)	.614	21 + 5 (12 + 0–27 + 6)	22 + 2 (12 + 0–27 + 6)	.948
Cervical length at start of therapy, mm[d]	21.3 ± 6.40	17.1 ± 12.0	.113	15.3 ± 7.42	13.4 ± 6.45	.312	18.4 ± 7.49	15.4 ± 9.91	.078
Cervical length Z-score at start of therapy[d]	−2.49 ± 0.55	−2.72 ± 0.96	.283	−2.55 ± 0.57	−2.78 ± 0.55	.148	−2.52 ± 0.55	−2.75 ± 0.79	.088

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TABLE 1
Baseline characteristics of the study population *(continued)*

Variable	Risk group[a]			Screening group[b]			Total population[c]		
	Pessary (n = 27)	Pessary and progesterone (n = 28)	*P* value	Pessary (n = 26)	Pessary and progesterone (n = 25)	*P* value	Pessary (n = 53)	Pessary and progesterone (n = 53)	*P* value
Funneling at start of therapy, n (%)	11 (40.7)	11 (39.3)	1	15 (57.7)	17 (68.0)	.637	26 (49.1)	28 (52.8)	.846
Tocolytics during course of pregnancy, n (%)	4 (14.8)	3 (10.7)	.705	7 (26.9)	4 (16.0)	.543	11 (20.8)	7 (13.2)	.438
Antenatal corticosteroids, n (%)	11 (40.7)	14 (50.0)	.676	13 (50.0)	12 (48.0)	1	24 (45.3)	26 (49.1)	.846
Premature preterm rupture of membranes at <37 weeks of gestation, n (%)	5 (18.5)	7 (25.0)	.798	7 (26.9)	4 (16.0)	.543	12 (22.6)	11 (20.8)	1
Gestational age at premature preterm rupture of membranes, wk + d ± SD[d]	29 + 6 ± 6 + 0	29 + 5 ± 6 + 0	.965	31 + 5 ± 3 + 0	34 + 0 ± 2 + 6	.251	31 + 0 ± 4 + 2	31 + 2 ± 5 + 2	.867
Mode of delivery, n (%)									
Spontaneous	15 (55.6)	15 (53.6)	.787	12 (46.2)	11 (44.0)	1	27 (50.9)	26 (49.1)	.882
Vaginal operative	1 (3.7)	0	.787	1 (3.85)	1 (4)	1	2 (3.77)	1 (1.89)	.882
Cesarean	11 (40.7)	13 (46.4)	.787	13 (50.0)	13 (52.0)	1	24 (45.3)	26 (49.1)	.882

Note: Baseline characteristics were analyzed with *t*-tests and χ^2-tests.

[a] Defined by previous preterm birth at >16 and <37 weeks of gestation, a history of surgical conization, or a previous cerclage because of a short cervix, all of which were characterized by a short cervical length at <10th percentile[19] that was detected by transvaginal sonography; [b] Defined by a cervical length at <3rd percentile[19]; [c] Separate for the treatment with either pessary alone or pessary combined with vaginal progesterone; [d] Data are given as mean ± SD; [e] Six patients in the pessary group and 5 patients in the combined group had a previous preterm birth and a conization or cerclage; here they are considered in both categories.

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Logistic regression was used to compare the primary and secondary outcomes between the pessary group and the group with pessary and additional vaginal progesterone. For birthweight and prolongation of pregnancy, a linear model was used. For the comparison of the number of days in the NICU, a zero-inflated Poisson regression model was used with the assumption that the treatment had an effect on the number of NICU days (Poisson part of the model) but not on the rate of NICU admission per se (n = 30). For all models, confounders such as the Z-score of CL at the time of treatment initiation, nulliparity, and the history of PTB were included as covariates. In contrast to absolute values, Z-scores of CL consider the normal range of values for each gestational week. The Z-scores were calculated based on the formula by Salomon et al.[19] For the zero-inflated Poisson regression the use of corticosteroids was included as an additional covariate in the Poisson parts of the models. In a separate analysis for the comparison of the number of days in the NICU (zero-inflated Poisson model), gestational age or birthweight was also included as an additional covariate. A variable that included the population group (risk vs screening) was included in all models for the total population. Probability values of $<.05$ were considered to indicate statistically significant differences between the 2 groups.

Results

The profile of the 106 patients is shown in Table 1; 53 women received a pessary, and 53 women received a pessary plus vaginal progesterone. Primigravid women were more common in the screening than the risk group (62.7% vs 14.5%). All 29 patients in both treatment arms who delivered between 24 and 33 + 6 weeks of gestation received corticosteroids that were administered only when the CL was <15 mm or a delivery <34 weeks of gestation was indicated. Patients who delivered at ≥34 weeks of gestation received corticosteroids in 21 of 76 cases (27.6%), in 11 of 40 patients (27.5%) in the pessary group, and 10 of 36 cases (27.8%) in the pessary plus progesterone group. There were no significant differences with respect to baseline characteristics (Table 1). Figure 1 shows the CL at the start of therapy separately for screening and risk populations and both treatment groups within the percentiles that were used for indication.

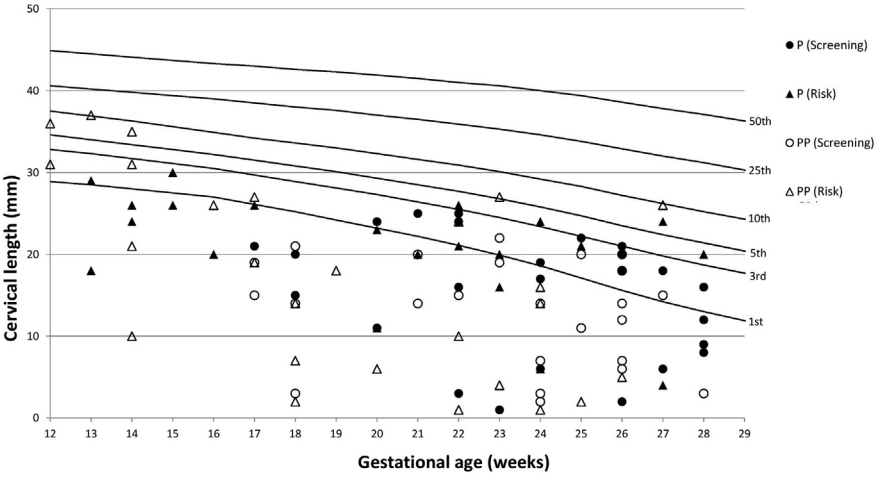
The rate of delivery at <34 weeks of gestation (primary outcome) was not significantly different: 13 of 53 patients (24.5%) were treated with pessary only, and 17 of 53 patients (32.1%) were treated with pessary and vaginal progesterone (odds ratio [OR], 1.29; 95% confidence interval [CI], 0.53−3.15; $P = .57$; Table 2).

There were also no significant differences in the rates of PTB at <28, 32, or 37 weeks of gestation (Table 2). This is reflected in the Kaplan Meier curves that show a trend of a longer prolongation in risk pregnancies that were treated with pessary only and in screening patients who were treated with pessary plus vaginal progesterone (Figure 2). Neither birthweight nor the duration of pregnancy prolongation differed significantly (Table 2). Composite poor neonatal outcome occurred in 8 of 53 neonates (15.1%) who were treated with pessary only and 10 of 53 neonates (18.9%) who were treated with pessary and vaginal progesterone (OR, 1.03; 95% CI, 0.34−3.09; $P = .96$; Table 2). One perinatal death occurred at 22 + 2 weeks of gestation in a patient with pessary and progesterone.

A low CL Z-score at the start of therapy showed a trend to correlate with PTB at <34 weeks of gestation (OR, 0.543; $P = .091$) for all pregnancies.

In total, 15 of 53 newborn infants (28.3%) in each group were admitted to the NICU (OR, 0.94, 95% CI, 0.39−2.25; $P = .89$). The average days of neonatal admission were 52.0 (range, 3-151) days in the pessary group compared with 46.5 (range, 9-130) days in the combined group ($\exp(\beta)$, 0.57; 95% CI, 0.50-0.65; $P < .0001$). Although the absolute numbers were small, the statistical difference remained in the subgroups of risk or screening patients (Table 2). Even when we controlled for gestational age or birth weight in the regression model the results did not change.

FIGURE 1
Cervical length at start of therapy



Cervical length within percentiles according to Salomon et al[19] in singleton pregnancies with a short cervical length at <3rd percentile detected by transvaginal sonography (*Screening*) or singleton pregnancies with a short cervical length at <10th percentile and a history of preterm birth, surgical conization, or a previous cerclage because of a short cervix (*Risk*), both treated with either pessary alone or pessary combined with vaginal progesterone.

P, pessary alone; *PP*, pessary combined with vaginal progesterone.

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TABLE 2
Outcome of the study population that was treated with cervical pessary or pessary combined with vaginal progesterone

Outcome	Risk group					Screening group					Total population				
	Pessary (n = 27)	Pessary and progesterone (n = 28)	Odds ratio	95% Confidence interval	*P* value	Pessary (n = 26)	Pessary and progesterone (n = 25)	Odds ratio	95% Confidence interval	*P* value	Pessary (n = 53)	Pessary and progesterone (n = 53)	Odds ratio	95% Confidence interval	*P* value
Primary outcome															
Delivery at <34 wk, n (%)	6 (22.2)	10 (35.7)	1.63	0.44–6.2	.46	7 (26.9)	7 (28)	0.88	0.23–3.23	.84	13 (24.5)	17 (32.1)	1.29	0.53–3.15	.57
Secondary outcomes															
Delivery, n (%)															
<28 Wk	1 (3.7)	4 (14.3)	2.33	0.21–53.76	.51	2 (7.7)	1 (4.0)	0.36	0.01–4.43	.44	3 (5.7)	5 (9.4)	0.98	0.18–5.61	.98
<32 Wk	3 (11.1)	6 (21.4)	1.11	0.18–6.91	.9	5 (19.2)	5 (20)	0.89	0.20–3.85	.88	8 (15.1)	11 (20.8)	1.1	0.37–3.30	.86
<37 Wk	10 (37.0)	14 (50)	1.25	0.36–4.26	.72	13 (50)	10 (40)	0.56	0.16–1.80	.33	23 (43.4)	24 (45.3)	0.91	0.40–2.05	.83
Composite poor outcome, n (%)	3 (11.1)	6 (21.4)	1.18	0.20–7.18	.85	5 (19.2)	4 (16.0)	0.76	0.16–3.41	.71	8 (15.1)	10 (18.9)	1.03	0.34–3.09	.96
Admission to neonatal intensive care unit, n (%)	6 (22.2)	9 (32.1)	1.51	0.41–5.66	.53	9 (34.6)	6 (24.0)	0.54	0.14–1.89	.33	15 (28.3)	15 (28.3)	0.94	0.39–2.25	.89
Neonatal admission time, d[a]	51.8 ± 37.7	47.6 ± 43.1	0.39[b]	0.31–0.50	< .01	52.1 ± 39.1	45.0 ± 54.5	0.61[b]	0.51–0.73	< .01	52.0 ± 37.1	46.5 ± 46.1	0.57[b]	0.50–0.65	< .01
Birthweight, g[a]	2919 ± 953	2668 ± 1010	−162.9[c]	−695.7–369.8	.54	2602 ± 907	2805 ± 966	277.2[c]	−267.3–821.65	.31	2763 ± 935	2734 ± 982	21.5[c]	−355.9–398.9	.91
Prolongation, d[a,d]	128 ± 46.8	113 ± 52.6	−9.41[c]	−35.74–16.91	.48	83.1 ± 45.3	93.7 ± 45.1	7.69[c]	−18.4–33.78	.56	106 ± 50.9	104 ± 49.7	−1.77[c]	−20.71–17.05	.85

[a] Data are given as mean ± SD; [b] Exponentiated regression coefficient (zero-inflated Poisson regression model); [c] Regression coefficient (linear regression model); [d] Interval between start of therapy and delivery.

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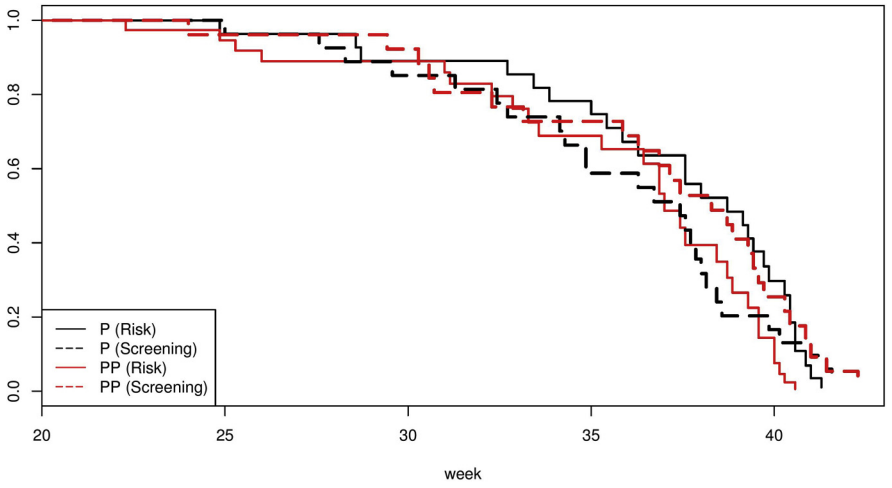
FIGURE 2
Kaplan-Meier curves



Curves show the prolongation of pregnancy of the risk population that was treated with either pessary or pessary plus vaginal progesterone and the screening population that was treated with either pessary or the combination of pessary and vaginal progesterone.

P, pessary alone; *PP*, pessary combined with vaginal progesterone.

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Comment

Principal findings

Findings of this study suggest preliminary justification for the benefit of combined use of a cervical pessary and vaginal progesterone, although it did not reduce the rate of PTB compared with singular therapy with cervical pessary alone. However, neonates whose mothers were treated with additional vaginal progesterone had a shorter NICU stay. Large studies are expected to be finalized that will compare the effect of both singular strategies[14,16,17] or are in progress to compare basic vaginal progesterone vs progesterone plus a cervical pessary (Matthew Hoffman Matthew et al, oral communication, February 2, 2016). Normally, multicenter studies take years to complete and even longer for results to be disseminated; in the meantime, patients should be informed and treated based on preliminary knowledge.

Meaning of the findings

The evidence that progesterone reduces the rate of PTB was first suggested by Papiernik-Berkhauer[7] in 1970 and by Keirse[26] in 1990. The synthetic 17-α-hydroxyprogesterone caproate (17-OHPC) has a long half-life and is administered intramuscularly on a weekly basis. Natural progesterone has a short half-life, is rapidly absorbed across the vaginal mucosa, and is administered daily.[27] The benefit of 17-OHPC as a preventive therapy in patients with a history of PTB remains controversial because the RCT of Meis et al[28] was questioned by the US Food and Drug Administration for its high baseline PTB rate in the placebo group (54.9%) and over safety issues.[27] Currently, another large multicenter RCT is in progress enrolling women with a history of PTB.[29] The use of natural progesterone to prevent PTB experienced a revival after the first RCT was published in 2003 by DaFonseca et al.[30] However, their selection of patients was not based on TVS. In another study, patients with a short CL were even excluded.[31] It was only when DaFonseca et al investigated the effect of vaginal progesterone in combination with TVS that the investigators were able to determine that PTB at <34 weeks of gestation could be reduced in patients with a short CL of <15 mm. Unfortunately, the study was not powered to detect a reduction in neonatal morbidity.[9] This further step was taken in the study by Hassan et al.[10]

A ring pessary was first suggested by Cross[8] in 1959 to prevent PTB. The availability of TVS[5] and the knowledge of a specific cervical pessary that enclosed the inner os[32] by a convex shape changing the angle between cervix and lower uterine segment, as demonstrated on magnetic resonance imaging,[33] revived interest in its use for patients with a short CL.[11] A RCT in singleton pregnancies with a short CL revealed a reduction in PTB at <34 weeks of gestation and improvements in neonatal outcome.[12] Alfirevic et al[34] retrospectively compared patients who were at risk for PTB with a short CL who had received a cerclage, vaginal progesterone, or a pessary; however, because of the design, these results should be interpreted with caution. Conflicting results were reported from a group in Hong Kong who found benefit in patients with high risk, but not in a still underpowered study with low risk-patients.[35,36]

Berghella et al[37] demonstrated a decrease of PTB rate at <35 weeks of gestation in singleton pregnancies with a CL of <25 mm that were treated by cervical cerclage. In this study, the reduction did not reach significance in patients with funneling or with a CL of <15 mm. After inclusion of data by Owen et al,[38] another metaanalysis by Berghella et al[39] showed a significant reduction in PTB of cerclage in singleton pregnancies that had both a previous PTB and a CL of <25 mm, even in the subgroup with a CL of <15 mm. Evidence that a cerclage is beneficial in patients without a previous PTB is still missing.[40]

Within our preselected risk group, 19 patients had a previous conization, and all had a short CL, although this has been observed differently.[41] The invasiveness of the conization might vary dependent on operative skills and the severity of disease. In addition, indications for referral may vary. In any case, in women with a history of conization, the CL detected by TVS is the most significant risk factor.[42] Because of local policy, some colleagues referred patients in the first trimester particularly if they had a

history of perinatal losses or early PTB. Because prophylactic cerclage could not prevent PTB in patients with a conization and a short CL,[42,43] we proposed treatment by a pessary and after 2011 pessary plus progesterone, although RCTs are lacking.[44]

All women in our at-risk group were already afraid of the consequences of an early PTB. They were informed about treatment options such as cerclage,[37-40] pessary,[34,44] and, from 2011 onward, vaginal progesterone.[10] After the informed-consent process, our patients preferred a pessary to a cerclage, likely because of the noninvasive nature of the pessary and the fact that it easily could be applied directly after TVS.

Clinical implications

A successful prevention of PTB should reduce both prematurity and neonatal morbidity.[45] Although our numbers are too small to reach significance for composite neonatal outcome, the shorter NICU stay of the neonates whose mothers were treated with a combined therapy suggests that these children experienced less severe morbidity. This interpretation is limited by a historic model, although the general policy and staff had not been changed during the observation period. DeFranco et al[46] found similar results: Neonates whose mothers had received vaginal progesterone spent on average of only 1.1 day in the NICU; neonates from mothers with expectant treatment spent an average of 16.5 days.

Research implications

We had hoped that the combination of cervical pessary and vaginal progesterone might have a complementary and more obvious additive benefit. This was not the case, but it is likely that, if a therapy is already effective in preventing PTB, any additional or marginal benefit of other interventions would be difficult to discern. This might be the same if a study starts with vaginal progesterone in all patients and then randomly adds a pessary. Our findings imply that a large number of patients will be required to show an improvement in neonatal outcome of a combined therapy, which makes it improbable that such trials will be completed soon.

To explain the reason that neonates in both subgroups had shorter NICU stays when vaginal progesterone was added deserves pathophysiologic considerations that can be found elsewhere.[47-54] There appear to be no long-term outcome data for vaginal progesterone. However, when progestogens were used in women with infertility, there was an increased rate of acute lymphoblastic leukemia and sympathetic nervous system tumors that was consistent with the fact that, as an accelerator of cell division, progestogens could increase the mutation rate through epigenetic changes.[55]

Strengths and weaknesses

In contrast to pharmacologic trials, pessary treatment cannot be blinded; however, analysis was blinded in our study from the clinician who was responsible for treatment and follow-up that included critical decisions regarding continuation or cessation of treatment.

It is disappointing that gynecologists, either in trials or in clinical practice, rarely do take part in team training or sometimes not even follow protocols. A lack of quality control may explain the reason that trials in different settings may fail. Already introduced audit procedures[56] should be limited not only to diagnostic tools[57] but also be implied for interventions and patient follow-up evaluations mainly when procedures are still novel. Compliance is a crucial issue. It had been shown, even in a national study, that "clinicians because of disbelief" either removed a pessary too early or inappropriately applied a cerclage instead of following the pessary arm of the study.[58] Although our study was small, the strength is that we avoided these limitations.

Unlike most studies, we did not use cut-offs for CL but percentiles[19] as a criterion for therapy. As already suggested, "reference ranges are more useful than single cut-off values for efficient prevention and management of PTB."[59] Numeric cut-offs are pragmatic for RCTs when patients are included at a certain gestational age, but the cervix does not change in steps but continuously. In addition, in private health care systems, patients are referred at varying gestational ages. Different percentile cut-offs could be chosen for interventions in screening and at-risk groups because cervical shortening progresses faster in at-risk groups.[60] Altogether, we regard the use of percentiles as a strength.

Our study has design limitations. The data were collected from patients who were referred by local gynecologists, which resulted in different gestational ages at treatment initiation or even a selection bias. There was no control group without intervention because these women required care based on the best information available, albeit imperfect. Last but not least, because of the small number of patients controlled by 1 specialist, our study can be regarded only as a pilot.

Next step in research

The Go-Net (Global Obstetrics Network) initiative was founded by international investigators in obstetrics or maternal and fetal medicine to standardize core outcomes for PTB among researchers, midwifes, and patients to unify their outcome parameters. In addition, several groups now have decided to combine their study results of pessary studies in a prospective metaanalysis. Similarly to the criteria for primary prevention of PTB,[61] 13 consensus outcomes were agreed to and have been incorporated into many trials in different countries. The full results have been submitted as Core Outcomes in Women's Health. Nevertheless, it will take years until studies that use these outcomes will be available for meta- or subgroup analyses.

In summary, any power analysis for future trials should consider the large number of patients that is necessary to confirm an additional benefit of a combined therapy and not to forget the importance of teaching and audit procedures. In the meantime, it seems reasonable to indicate both treatment strategies in patients at high risk of perinatal loss or early PTB. Health care providers and policy makers should realize that the clinical risks and costs of TVS, even in patients without previous PTB,[62]

and of both preventive strategies are relatively low[63-65] compared with tertiary procedures that frequently are initiated too late. Even more important than cost reduction is the need to prevent the suffering of parents and children as a consequence of prematurity. ■

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