

ABSTRACT

Objective: To survey how United States (US) physicians screen, define, and treat a short cervix to prevent preterm birth (PTB).

Study Design: Practicing physicians in the US were recruited across the 9 US Census divisions for a cross-sectional, web-based survey recruited from a blend of Nielsen Company and preferred partner online physician panels. The survey consisted of 27 questions, and the fielding period was April 30–May 11, 2016. The primary outcome was the use of progestogens (i.e., 17 alpha-hydroxyprogesterone caproate or vaginal progesterone) in women with singleton gestations and a short cervix.

Results: Overall, survey completers (N = 500) were predominantly OB/GYNs (91%), white (76%), non-Hispanic (96%), and male (55%). The mean age was 49 years, and 6% were maternal-fetal medicine specialists. Physicians reported that a median of 90% of their pregnant patients are screened for short cervical length (SCL); 81% use transvaginal ultrasound (TVU). The most common definition for short cervix was ≤ 25 mm regardless of pregnancy history. Physicians rely on multiple sources of evidence to guide their patient care, with clinical guidelines (83%) and published research (70%) most frequently reported. Ninety-eight percent of physicians treat pregnant patients with SCL; 95% report synthetic and/or natural progesterone use, either alone or in combination with other treatment modalities. If cost were no issue, 47% of physicians would choose a vaginal progesterone preparation to treat patients with SCL and 45% a synthetic progesterone product.

Conclusion: US guidelines recommend TVU as the preferred method for cervical length screening for pregnant patients, yet not all physicians reported using this method. Ninety-five percent of physicians surveyed use progestogens to treat SCL, with approximately half using a synthetic and half using natural progesterone. Although most noted following clinical guidelines in treating SCL, one-third reported never using vaginal progesterone as recommended to treat women with SCL and no history of spontaneous PTB. PTB remains a leading cause of infant mortality in the US, and current guidelines have been unable to improve use of the preferred progesterone formulation (i.e., vaginal progesterone) in treating SCL to prevent PTB.

BACKGROUND

- A sonographic short cervix is a strong predictor of PTB,¹ a leading cause of perinatal morbidity and mortality.
- In women at risk for PTB, vaginally administered progesterone, a natural progesterone, is associated with lower rates of preterm delivery, delayed cervical shortening, and improved neonatal outcomes relative to no treatment.^{2,8}
- Whereas vaginal progesterone has shown efficacy in reducing cervical shortening, this effect has not been observed with progestin, a synthetic progesterone.^{9,10}
- US clinical guidelines recommend universal cervical length screening at 18 to 24 weeks gestation and recommend the use of vaginal progesterone for sonographic short cervix in pregnant women with no history of spontaneous PTB.¹¹
- Although it is assumed that many US physicians screen for cervical length and use vaginal progesterone as recommended, the extent to which clinicians have fully adopted these practices is unclear.

OBJECTIVE

- To conduct a physician survey to evaluate how health care providers in the US screen for, define, and treat SCL to prevent PTB, with a particular focus on how commonly vaginal progesterone has been adopted as standard practice in treating the condition.

METHODS

Study Design and Population

- A cross-sectional, web-based survey of physicians in the US seeing pregnant patients with SCL was conducted.
- Survey respondents were recruited from a blend of the Nielsen Company's OB/GYN panel and Harris, Sermo, and WebMD online physician panels.
 - Inclusion criteria included respondents aged ≥ 25 years with primary practices in the US who were actively seeing adult pregnant patients with a mid-trimester diagnosis of SCL.
- Respondents' geographic region was monitored to ensure a balanced sample across nine geographic regions defined by US Census division.

Survey Instrument

- The 27-item survey instrument assessed the following:
 - Physicians' demographic and practice characteristics
 - SCL screening practices (e.g., screening methods and SCL cut-off scores)
 - SCL treatment patterns (e.g., treatment choices used in clinical practice, sources of information guiding treatment decisions, and treatment preferences and satisfaction)

Analytic Methods

- The data analyses were descriptive.
 - Means, standard deviations, medians, and ranges were reported for continuous variables; frequencies and percentages were reported for categorical variables.
 - No missing data were imputed.
- Screening and treatment patterns were stratified by "practice setting," a derived variable defined by practice type (teaching hospital or other) and practice location (urban, suburban, or rural).
- All statistical analyses were conducted using SAS Version 9.4 (SAS Institute; Cary, NC).

RESULTS

Study Population

- Invitations for the survey were sent to 13,197 panel members, and 693 physicians started screening (Figure 1). The survey was closed after 500 physicians completed the survey.
- Sample characteristics were as follows:
 - Overall, 91% of physicians were OB/GYNs, gynecologists, or obstetricians; 6% were maternal-fetal medicine physicians; 2% were family practitioners; and < 1% were other physicians.
 - The sample was mostly white (76%), non-Hispanic (96%), and male (55%). The mean (SD) age was 49 (10) years.
- Overall, 36% of respondents reported that 10% to 24% of their adult female patients become pregnant in an average year, and 49% of respondents reported that 10% to 24% of the pregnancies managed in their adult pregnant patients were considered high risk.

Screening and Treatment Patterns

- Physicians reported that a median of 90% of their adult pregnant patients receive screening for cervical length during their pregnancy.
 - TVU is the most common method used for screening (81%), followed by transabdominal ultrasound (TAU) (40%); 23% used both for screening (Figure 2).
 - Most physicians (94%) reported having TVU machines in their practices.
- The most common cut-off value for short cervix was ≤ 25 mm, regardless of practice setting and history of spontaneous PTB (59% for patients without and 62% for patients with such a history) (Figure 3).
- Nearly all physicians (95%) reported using some form of progesterone to treat pregnant women with SCL (Table 1).
 - Most physicians (78%) reported using natural progesterone; 63% reported using synthetic progesterone.
 - Few physicians (3%) did not use progesterone but reported using some other form of treatment to prevent PTB in pregnant women with SCL, and 2% reported using no treatment.
- Physicians were asked about how frequently they prescribe vaginal progesterone for pregnant women with SCL (Table 2).
- Approximately half of the sample (49%) reported using compounded progesterone products, including the synthetic progestin hydroxyprogesterone caproate and natural compounded progesterone, to treat single-gestation patients with SCL.
- Overall, 89% of physicians reported that the products they used were moderately or a little efficacious, 9% reported the products they used to be very or extremely efficacious, and 2% reported that the products they used were not at all efficacious.
- Physicians reported using multiple sources of information when making decisions about treatment for patients with SCL, with 83% reporting use of established clinical guidelines, 70% using published research (on the disease or treatments), 63% using clinical judgment, 51% using information from colleagues or other practice area experts, and 24% considering the patient's insurance.

Reimbursement and Treatment Decisions

- When asked which treatment they would prefer using in treating SCL to prevent PTB if reimbursement was not an issue, 47% of physicians noted they would choose a vaginal progesterone preparation, including 7% who would choose a compounded progesterone.
- Another 45% would choose a synthetic progestin product, including 6% who would choose a compounded preparation.

Figure 1. Respondent Disposition

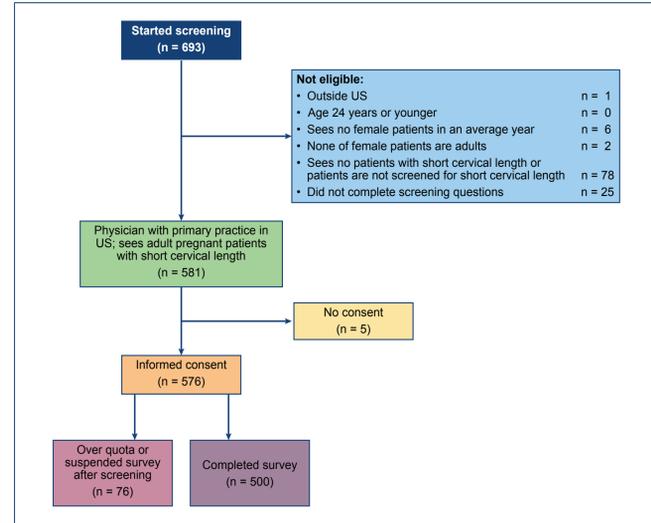
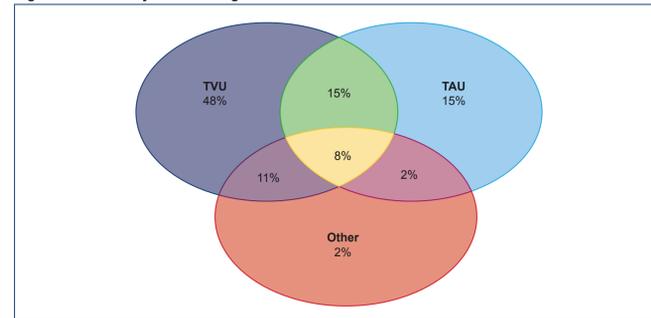


Figure 2. Summary of Screening Methods for SCL



Note: Percentages do not sum to 100% due to rounding.

Table 1. Summary of Treatment Patterns for Treating Single-Gestation Patients With a Short Cervix to Prevent PTB

| Category and Type of Treatment | Teaching Hospital (n = 66) | Other Practice Type*, Urban (n = 137) | Other Practice Type*, Suburban (n = 228) | Other Practice Type*, Rural (n = 69) | Overall (N = 500) |
|-------------------------------------------------------------|----------------------------|---------------------------------------|------------------------------------------|--------------------------------------|-------------------|
| No treatment | 2 (3%) | 2 (1%) | 4 (2%) | 2 (3%) | 10 (2%) |
| Any progesterone treatment* | 61 (92%) | 132 (96%) | 218 (96%) | 63 (91%) | 474 (95%) |
| Natural vaginal progesterone ^b | 50 (76%) | 107 (78%) | 178 (78%) | 54 (78%) | 389 (78%) |
| Synthetic intramuscular progestin ^c | 39 (59%) | 87 (64%) | 151 (66%) | 39 (57%) | 316 (63%) |
| Any other treatments ^d | 39 (59%) | 69 (50%) | 105 (46%) | 38 (55%) | 251 (50%) |
| Solely other treatments, without any progesterone treatment | 3 (5%) | 3 (2%) | 6 (3%) | 4 (6%) | 16 (3%) |

Note: Physicians could select more than one response.

* "Other practice type" comprises all practice types except teaching hospital.

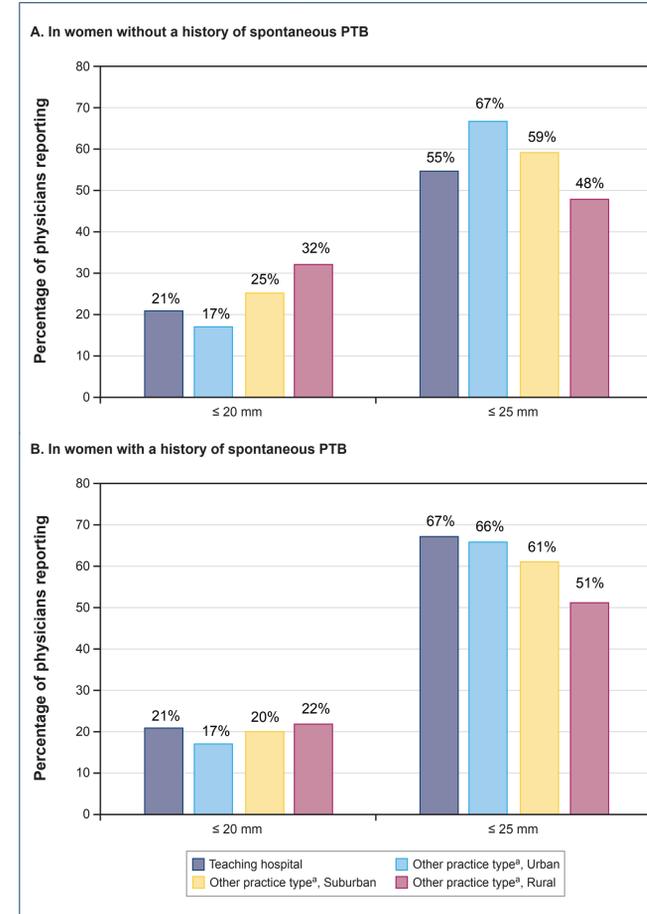
^b Progesterone treatments are Crinone or Prochieve gel, Endometrin vaginal insert, Prometrium capsules, Utrogestan capsules, Progesterone capsules, Cyclogest capsules, pessary plus progesterone, compounded progesterone, Makena 17-OHP injection, and compounded hydroxyprogesterone caproate injection.

^c Natural progesterones are Crinone or Prochieve gel, Endometrin vaginal insert, Prometrium vaginal insert, Prometrium capsules, Utrogestan capsules, Progesterone capsules, Cyclogest capsules, pessary plus progesterone, and compounded progesterone.

^d Synthetic progestogens are Makena 17-OHP injection and compounded hydroxyprogesterone caproate injection.

^e Other treatments are prophylactic cervical cerclage and/or stitched cervix, pessary only, and other.

Figure 3. Cut-off Length Used in Defining Short Cervix



* "Other practice type" comprises all practice types except teaching hospital.

Note: Physicians were asked to select one cut-off value generally used in defining SCL. The two most common cut-offs are presented in the figure.

Table 2. Frequency of Prescribing Vaginal Progesterone to Various Patient Populations With SCL to Prevent PTB

| Patient Population | N | Never | Always |
|-------------------------------------------------------------------------------------------------------------------------|-----|-------|--------|
| In singleton gestations with no history of spontaneous PTB or mid-trimester loss | 500 | 33% | 18% |
| In singleton gestations with a history of spontaneous PTB or mid-trimester loss | 500 | 24% | 24% |
| In women with multiple gestations | 500 | 53% | 9% |
| Only with symptomatic pregnant patients with a short cervix (e.g., PTB or preterm rupture of membranes) | 500 | 38% | 20% |
| Women with asymptomatic short cervix | 500 | 27% | 21% |
| With all or nearly all pregnant patients, regardless of spontaneous PTB history or singleton versus multiple gestations | 495 | 36% | 13% |
| Women with previous cervical surgery | 494 | 40% | 14% |
| A history of cervical trauma | 494 | 49% | 11% |

Note: Physicians were asked to report what percentage of their patients diagnosed with SCL were prescribed vaginal progesterone to prevent PTB. "Always" was defined as the percentage of respondents who reported that they treated 100% of patients in a given population with vaginal progesterone. "Never" was defined as the percentage of respondents who responded that they treated 0% of the patients in a given population with vaginal progesterone.

DISCUSSION

- The US guidelines recommend routine screening in pregnant patients for SCL via TVU and note that TAU is not reliable or reproducible for universal cervical length screening.¹¹⁻¹³ Educational activities may be needed for physicians who use TAU (40%) and nonultrasound screening methods, to ensure that screening and treatment of pregnant patients with SCL are in line with current guidelines.
- For pregnant women with sonographic short cervix and no history of spontaneous PTB, US clinical guidelines recommend use of vaginal progesterone.¹¹⁻¹³ However, there are no vaginal progesterone products approved by the US Food and Drug Administration that are available to treat women with SCL. Clinicians are left to decide on their own how to treat women with SCL.
- The current study is characterized by several limitations, including a cross-sectional design and potential biases associated with a voluntary survey using a convenience sample and collecting self-reported data. Nevertheless, the sample was geographically diverse, and the overall sample size provides confidence in the robustness of these findings.

CONCLUSIONS

- US guidelines recommend TVU as the preferred method for cervical length screening for pregnant patients, yet not all physicians reported using this method.
- Most physicians surveyed use progesterone to treat SCL, with approximately half using a synthetic and half using natural progesterone. Although most noted following clinical guidelines in treating SCL, one-third reported never using vaginal progesterone as recommended to treat women with SCL and no history of spontaneous PTB.
- PTB remains a leading cause of infant mortality in the US, and current guidelines have been unable to improve use of the preferred progesterone formulation (i.e., vaginal progesterone) in treating SCL to prevent PTB.

REFERENCES

- To et al. Ultrasound Obstet Gynecol. 2006;27(4):362-7.
- Fonseca et al. N Engl J Med. 2007;357(5):462-9.
- DeFranco et al. Ultrasound Obstet Gynecol. 2007;30(5):697-705.
- Majhi et al. J Obstet Gynaecol. 2009;29(6):493-8.
- Cetingoz et al. Arch Gynecol Obstet. 2011;283(3):423-9.
- Hassan et al. Ultrasound Obstet Gynecol. 2011;38(1):18-31.
- Norwitz et al. Rev Obstet Gynecol. 2011;4(2):60-72.
- Romero et al. Ultrasound Obstet Gynecol. 2016 May 4. DOI: 10.1002/uog.15953
- O'Brien et al. Ultrasound Obstet Gynecol. 2009;34(6):653-9.
- Durnwald et al. Am J Obstet Gynecol. 2009;201:410.e1-5.
- Medicaid Health Plans of America. <https://access.tarrantcounty.com/content/dam/main/public-health/PH%20DOCUMENTS/17P/PTBissueBrief111714MedicaidHPA.pdf>. Accessed July 1, 2016.
- Society for Maternal-Fetal Medicine Publications Committee et al. Am J Obstet Gynecol. 2012;206(5):376-86.
- American College of Obstetricians and Gynecologists. Obstet Gynecol. 2012;120(4):964-73.

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