Progesterone for the prevention of preterm birth

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Use of progesterone treatment for the prevention of recurrent preterm birth: identification of obstacles to change

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American Journal of Perinatology. 2010 Mar;27(3):241-9

Abstract

Progesterone treatment has proven to be effective in preventing recurrent preterm birth. The use of progesterone varies widely between different obstetric clinics in the Netherlands. The study aimed to identify factors that hamper or facilitate the use of progesterone to create an implementation strategy. A Web-based survey was developed containing questions on socio-political factors, organizational factors, knowledge, and attitude. This survey was spread among 212 gynecologists, 203 midwives, and 130 women with a recent preterm birth. Response rates were 46% for gynecologists, 57% for midwives, and 78% for patients. Twenty-five percent of gynecologists were prescribing progesterone, 21% of midwives would recommend progesterone, and 54% of patients were willing to undergo treatment in future pregnancies. Specific factors hampering implementation for gynecologists were working in nonteaching hospitals and absence of progesterone treatment in local protocols. For midwives and patients, unfamiliarity with progesterone was the most notable finding. The major reason for failure of implementation of progesterone treatment to prevent recurrent preterm birth is absence of this treatment in protocols and lack of familiarity with this treatment in midwives and patients. This may be overcome through adjustment of clinical protocols on regional and national levels.

Introduction

Preterm birth is the most important cause of perinatal morbidity and mortality in the Western world. It affects 12,000 pregnancies per year in the Netherlands and over half a million pregnancies yearly in the United States[1-3]. Women with a history of preterm birth are at three- to fourfold increased risk of delivering before 37 weeks of gestation in a subsequent pregnancy[4, 5]. In 2003, evidence became available that administration of progesterone is a highly effective intervention in this high-risk subgroup of women.[6, 7]

The role of progesterone in the process of preterm birth has been explored and debated for many decades. Recently, there has been a renewed interest after the publication of two randomized controlled trials on the prevention of recurrent preterm birth with progesterone in 2003 and a meta-analysis in 2005.[6-8] The randomized clinical trials of Meis et al and Da Fonseca et al, the first using weekly intramuscular injections and the second daily vaginal suppositories, both showed that progesterone administration between 20 and 36 weeks of gestation reduced the risk of delivery before 37 weeks in women with a previous preterm birth substantially (relative risk 0.66, 95% confidence interval 0.54 to 0.81 and relative risk 0.49, 95% confidence interval 0.25 to 0.94, respectively).[6, 7]

After the effectiveness of this intervention became apparent, 12 obstetric departments in the Netherlands agreed on adoption of this evidence in clinical practice. However, a prospective registration over 3 years of all patients treated in these 12 centers according to the new strategy (i.e., weekly intramuscular injections) showed a substantial variability in the use of treatment. The treatment was reasonably well implemented in two academic hospitals, with over 75% of patients being treated according to the new protocol, but in nonacademic hospitals, this was only the case in a small part of the patients. Reasons for this noncompliance were unknown.

Although generating knowledge on the effectiveness of treatments is the first step in improving patient outcome, the implementation of this knowledge is a second and equally important step. Our study aim was to identify factors that either facilitate or hamper the implementation of progesterone treatment, an evidence- based intervention for the prevention of recurrent preterm birth. This knowledge was used to develop an implementation strategy.

Methods

Study Design and Population

To identify factors that can hamper or facilitate implementation, we developed a questionnaire to assess the knowledge and attitude of 100 gynecologists, 100 midwives, and 100 patients. We invited all gynecologists with surnames starting with the letters A to D who were registered in the database of the Dutch Society for Obstetrics and Gynecology (NVOG). In doing so, we randomly approached doctors from both clinics that had participated in the previous adoption of the protocol and clinics that had not. As we anticipated a response rate of ~50%, we initially invited 217 gynecologists to participate. All were contacted through e-mail and were sent a link to a Web-based survey.

Midwives were contacted through e-mail addresses that were available on the Web sites of midwife practices in the Netherlands. The Web sites were either located through the Web site of the Dutch Royal Organization of Midwives or through the Dutch national telephone book. In addition, five randomly chosen circles of midwives spread around the Netherlands were contacted to collect individual e-mail addresses of their members. An e-mail containing a link to a Web-based survey was sent to a total of 200 addresses.

Patients were identified from delivery records in two academic hospitals, three nonacademic teaching hospitals, and one nonteaching hospital. As participation of patients in this study required ethical approval, we chose to invite patients from a limited number of hospitals. Five of these clinics had participated in the 2004 adoption of the protocol that was initiated by the University Medical Centre in Utrecht and the Academic Medical Centre in Amsterdam. All women who could be identified to have

had a spontaneous preterm birth <34 weeks that occurred in one of these six clinics in 2006 were contacted by telephone. Women with an iatrogenic preterm delivery were excluded. Only women who were currently pregnant or had a desire to become pregnant in the future were invited to participate in the study. For this part of the study, approval of a medical ethics committee was obtained. Participating women received an e-mailed invitation to take part in an online Web-based survey or a paper questionnaire was sent to their postal address. As all women were contacted by telephone prior to receiving the questionnaire, we expected a response rate of 75%. Therefore, questionnaires were sent to a total group of 130 women. All questionnaires incorporated in this study were sent and returned between April and December 2007.

Questionnaire Development

First, a panel of five experts defined potential facilitators and limitations of implementation. For classification of these factors, a framework was used that distinguishes between sociopolitical factors (i.e., opinion stated by opinion leaders in the field, comments in international journals, opinion of experts within the own department, attitude of the head of the department), organizational factors (i.e., logistic problems in obtaining the medication, failing identification of women with a previous preterm birth, insurance problems), factors within the user of the new technique (i.e., lack of knowledge on the risk of recurrence of preterm birth, lack of knowledge on the potential benefit of progesterone treatment, disbelief in the available evidence at the doctor or patient level, time restrictions for adequate counseling, anxiety for potential toxicological agents, skills and habits of the potential user), and factors within the innovation to be implemented itself (i.e., impracticality to be treated on a weekly basis within the given outpatient settings).[9] Furthermore, two focus group discussions were held with gynecologists, midwives, and a representative from a patient organization (association of parents of preterm children [VOC]). With this information, a structured and extensive interview was designed that was administered to 10 gynecologists, 10 midwives, and 10 patients. Based on the results of these interviews, validity, clarity, and internal consistency of the questions were assessed and a questionnaire was developed, containing both open-ended and multiple-choice questions.

Questionnaires

The questionnaire that was sent to gynecologists contained 37 questions on five major subjects: preterm birth, prevention of preterm birth, progesterone, obstacles in the field, and personal characteristics. Questions were mainly aimed at assessing knowledge, experience, habits, and preferences. Midwives received a similar, but condensed version of the survey with 22 questions. Because midwives generally do not initiate treatment for the prevention of recurrent preterm birth, the primary goal in this group was to assess knowledge and attitude toward different treatments.

The patient questionnaire contained 27 similar, but adjusted questions on the same subjects. Focus in this group was predominantly on knowledge and preferences.

Statistical Analysis

Results are reported as absolute numbers and percentages or by mean/median and standard deviation. For each characteristic, the odds of whether or not a respondent was willing to use progesterone was calculated by using odds ratios and 95% confidence intervals, as well as Student t test for continuous variables. Factors that were statistically significant in univariate analysis were incorporated into a multivariate analysis.

Survey Methods

For the digital version of the survey, we used a Web based provider of survey software (QuestionPro, Seattle, WA). In case of no response, a reminder was sent 3 weeks after the initial sending of the survey invitation. This was repeated after another 3 weeks. Responses were collected through computer-generated reports 3 weeks after the last reminder.

For the women in the patient group who preferred receiving the questionnaire by postal service, paper versions of the survey were generated, which were identical to the digital survey in both content and layout. The paper survey was resent in case of no response after 4 weeks.

Results

Gynecologists

Out of the 212 gynecologists who were initially contacted, 93 finished the online survey. Of the remaining 119 people, nine returned an e-mail stating that they were not currently active in the obstetric field and therefore not eligible for participation. Five others sent e-mails saying they were not willing to participate for various reasons (e.g., lack of trust in Web-based data exchange, dissatisfaction with the content of the survey). One hundred five gynecologists did not finish the survey or did not respond. The response rate among gynecologists was therefore 46% (93/203). Nonresponders did not differ from the responding group with respect to center (academic or nonacademic) or participation in the 2004 initiated implementation of progesterone treatment in that center.

Of all respondents, 13 gynecologists (14%) were unaware of the beneficial role of progesterone in the prevention of preterm birth. Of the remaining 80 respondents, 70% had obtained information on the subject from scientific publications, 68% from colleagues, and 46% from conferences. Nineteen respondents said that offering progesterone treatment for the prevention of recurrent preterm birth was part of their center's protocol. Of the remaining 74 respondents who stated that progesterone treatment was not in their center's protocol, 41 said that they would like to prescribe progesterone nevertheless. A total of 23 gynecologists (25%) actually prescribed

progesterone on a regular basis. Factors that may determine the frequency of applying progesterone treatment are displayed in Table 1. Odds ratios in this table reflect frequent use versus rare or no use of progesterone.

Factors associated with rarely or never prescribing progesterone were: working in a nonteaching hospital; rarely or never screening for bacterial vaginosis in patients with a history of preterm birth; not having progesterone treatment in the local protocol; and not feeling supported by the clinic and opinion leaders in the field. After multivariable

Table 1 Factors determining gynecologists' frequency of prescribing progesterone to prevent recurrent preterm birth

	Frequently prescribing progesterone (n=23)	Rarely/never prescribing progesterone (n=70)
General characteristics		
Practice		
Academic	10 (38%)	16 (62%)
Non-academic teaching	12 (30%)	28 (70%)
Non-teaching	1 (4%)	26 (96%)
Estimated number of patients with history of preterm birth <34 wks treated in clinic per year	mean 157.2 (±141.1)* median 80.0 (12-480)†	mean 94.0 (±133.2)* median 70.0 (10-278)†
Implementation of new treatment within clinic		
<2 yrs	4 (24%)	13 (76%)
2-5 yrs	2 (29%)	5 (71%)
after issue of national guideline	3 (13%)	21 (88%)
other/unknown	14 (31%)	31 (69%)
Age		
<40 yrs	8 (22%)	29 (78%)
41-50 yrs	7 (22%)	25 (78%)
>50 yrs	8 (33%)	16 (67%)
Knowledge of preterm birth (estimates made by interviewed gynecologists)		
Estimated incidence preterm birth	mean 9.0% (±3.9)* median 10.0% (3-19)†	mean 10.7% (±6.1)* median 10.0% (4-25)†
Estimated incidence mortality	mean 8.5% (±9.0)* median 7.5% (0.4-37)†	mean 10.5% (±9.4)* median 8.0% (1-30)†
Estimated incidence handicaps at age 10	mean 30.7% (±19.5)* median 30.0% (5-79)†	mean 37.2% (±23.1)* median 31.5% (5-82)†
Estimated recurrence risk	mean 21.8% (±9.8)* median 20.0% (10-57)†	mean 21.8% (±11.8)* median 20.0% (5-46)†
Habits in treatment		
Frequently applying primary cerclage	16 (12%)	46 (88%)
Frequently screening for bacterial vaginosis	18 (32%)	38 (68%)
Attitude towards treatment		
Subjective number allowed to treat to prevent one preterm birth	mean 16.2 (±18.2)* median 10.0 (1-70)†	mean 29.3 (±53.4)* median 10.0 (1-123)†
Belief in treatment safety for child	13 (33%)	27 (68%)
Belief in treatment safety for mother	17 (29%)	41 (71%)

analysis, absence of progesterone treatment in the local protocol and working in a nonteaching hospital remained significant factors.

Midwives

Two hundred three e-mail invitations were sent to midwives. Eighteen e-mail addresses turned out to be nonexistent or inaccessible. Three persons responded stating that they were not, or no longer, active as a midwife. A total of 103 midwives finished the online survey, yielding a response rate of 57% (103/182).

	Univariate analysis Odds Ratio (95% CI)/p-value	Multivariate analysis Odds Ratio (95% CI)
	1.0 0.69 (0.24 to 1.9) 0.06 (0.01 to 0.53)	0.04 (0.002 to 1.0)
	p=0.067	
	1.0 1.3 (0.18 to 9.5) 0.46 (0.09 to 2.4) 1.5 (0.41 to 5.3)	
	1.0 1.0 (0.32 to 3.2) 1.8 (0.57 to 5.8)	
	p=0.213	
	p=0.376	
	p=0.221	
	p=0.986	
	1.2 (0.44-3.2)	
	3.0 (1.0-8.7)	0.68 (0.14-3.4)
	p=0.366	
	1.4 (0.55 to 3.8)	
	1.1 (0.38 to 3.2)	

Table 1 (*Continued*)

	Frequently prescribing progesterone (n=23)	Rarely/never prescribing progesterone (n=70)
Clinical environment		
Support of clinic	19 (41%)	27 (59%)
Progesterone in protocol	16 (84%)	3 (16%)
Support of opinion leaders in the field	19 (31%)	42 (69%)
Obstacles in practice		
Time	4 (57%)	3 (43%)
Insurance	2 (15%)	11 (85%)
Pharmacy	5 (26%)	14 (74%)
Other	3 (14%)	19 (86%)
None	14 (28%)	36 (72%)
Knowledge of treatment		
Estimated relative risk		
0.5-0.7	18 (44%)	23 (56%)
<0.5	2 (13%)	13 (87%)
>0.7	0	8 (100%)
do not know	3 (19 %)	13 (81%)

* Standard deviation; † 5th - 95th percentile; N/A: not applicable

Fifty-three respondents (51%) in this group were unaware of the effectiveness of progesterone in preventing preterm birth. In the remaining 50 respondents, information on the subject was most often obtained from colleagues (50%) or scientific publications (36%). Of all midwives with previous knowledge of progesterone treatment, 20% said that they would not recommend progesterone if an eligible patient came to them for advice, 44% said that they would recommend progesterone, whereas the remaining 36% had no opinion.

No factors could be identified that were of any influence on midwives' knowledge of and attitude toward treatment with progesterone. Factors that may determine midwives' inclination to recommend progesterone treatment are displayed in Table 2.

Patients

One hundred eighty patients from five different hospitals were contacted by telephone. Patients with a desire to become pregnant in the future, or with a current pregnancy, were asked to participate in the survey. Out of the 132 women meeting these criteria, 130 agreed to participate. A paper version of the survey was sent to 56 women; 74 received an e-mail containing a link to the Web-based survey. Three e-mails could not be delivered due to technical problems. A total of 99 women responded to the survey. The response rate was therefore 78%, with rates of 77% and 79% for post and e-mail, respectively.

Of all treatment strategies mentioned in the questionnaire (bed rest, prophylactic hospital admission, primary cerclage, cervical length measurement, secondary cerclage, progesterone treatment, and screening for bacterial vaginosis with subsequent antibiotic

	Univariate analysis Odds Ratio (95% CI)/p-value	Multivariate analysis Odds Ratio (95% CI)
	7.6 (2.4 to 23.5)	4.5 (0.62 to 33.2)
	28.2 (6.7 to 115.6)	71.9 (7.4 to 702.3)
	3.2 (1.0 to 9.8)	8.2 (0.63 to 106.2)
	4.7 (1.1 to 20.5)	2.5 (0.12 to 52.2)
	0.51 (0.12 to 2.3)	
	1.1 (0.37 to 3.4)	
	0.40 (0.12 to 1.4)	
	1.5 (0.57 to 3.8)	
	1.0	
	0.31 (0.06 to 1.5)	
	n/a	
	0.46 (0.12 to 1.8)	

treatment), bed rest was best known (79%) and progesterone treatment was least known (27%). Most respondents were willing to undergo screening for bacterial vaginosis with, if necessary, subsequent antibiotic treatment (87%). Primary cerclage was the least popular treatment, with 49% willing to try this. Fifty-four percent stated that they were willing to undergo progesterone treatment in a future pregnancy. In the group with previously existing knowledge of progesterone treatment, this percentage was significantly higher than in the group without previous knowledge (74% versus 46%, odds ratio 3.4, 95% confidence interval 1.3 to 8.8). Factors that may determine patients' willingness to undergo progesterone treatment are displayed in Table 3.

Willingness to undergo progesterone treatment was lower in women with a lower level of education, a more advanced gestational age of the most recent or most severe preterm birth, and disbelief in the safety of treatment. After multivariate analysis, low educational level and more advanced gestational age of the most recent preterm birth remained significant factors.

Discussion

Although in the results of the questionnaire no factors stood out that influence midwives' attitude toward progesterone treatment, it was striking that many midwives were unfamiliar with this strategy. Notable also was that, when asked whether patients consulted them for advice on a subsequent pregnancy following a preterm birth, 41% of midwives said they were consulted regularly. On the question how much information they would provide in

Table 2 Factors determining attitudes towards progesterone to prevent recurrent preterm birth in midwives with previous knowledge of progesterone treatment

	Would recommend progesterone (n=22)	Would not recommend progesterone or no opinion (n=28)	Univariate analysis Odds Ratio (95% CI)/p-value
General characteristics			
Age			
<30 yrs	8 (42%)	11 (58%)	1.5 (0.39 to 5.4)
31-40 yrs	6 (33%)	12 (67%)	1.0
>40 yrs	8 (62%)	5 (38%)	3.2 (0.75 to 13.7)
Number of articles read per month			
<1	8 (44%)	10 (56%)	1.0
1-5	10 (40%)	15 (60%)	0.83 (0.25 to 2.8)
>5	4 (57%)	3 (43%)	1.7 (0.31 to 8.8)
Number of deliveries per practice per year	Mean 509.8 (±580.9)* median 300.0 (100-2100)†	mean 335.5 (±211.6)* median 350.0 (65-1200)†	p=0.192
Number of deliveries per midwife per year	Mean 91.7 (±34.9)* median 90.8 (40-188)†	mean 88.3 (±25.7)* median 88.8 (50-150)†	p=0.695
Percentage of referrals for (threatened) preterm birth	Mean 3.9% (±3.1%)* median 3.1% (0-10)†	mean 5.9% (±7.1%)* median 4.2% (2-40)†	p=0.302
Frequently consulted for information	8 (40%)	12 (60%)	0.76 (0.25 to 2.4)
Knowledge of treatment			
Estimated relative risk	Mean 0.47 (±0.18)* median 0.40 (0.2-0.8)†	mean 0.52 (±0.25)* median 0.50 (0.1-1.0)†	p=0.472
Attitude towards treatment			
Treatment is safe for child			
agree	8 (50%)	8 (50%)	1.0
disagree	0	6 (100%)	n/a
unknown	14 (50%)	14 (50.0%)	1.0 (0.30 to 3.3)
Treatment is safe for mother			
agree	8 (44%)	10 (56%)	1.0
disagree	0	5 (100%)	n/a
unknown	14 (52%)	13 (48%)	1.1 (0.32 to 3.6)
Knowledge of preterm birth			
Estimated incidence of preterm birth	Mean 10.2% (±6.7)* median 10.0% (2-30)†	mean 9.3% (±7.1)* median 8.0% (1-35)†	p=0.665
Estimated incidence mortality	Mean 18.0% (±16.8)* median 10.0% (1-60)†	mean 16.3% (±14.4)* median 10.0% (5-60)†	p=0.710
Estimated incidence handicaps at age 10	Mean 48.2% (±23.6)* median 47.5% (10-90)†	mean 41.6% (±24.8)* median 40.0% (3-80)†	p=0.347
Estimated recurrence risk			
20+0 - 27+6 wks	mean 40.1% (±20.3)* median 40.0% (10-80)†	mean 30.0% (±17.4)* median 27.5% (5-70)†	p=0.065
28+0 - 33+6 wks	mean 26.9% (±17.7)* median 24.0% (9-70)†	mean 21.9% (±12.7)* median 20.0% (3-50)†	p=0.25
34+0 - 36+6 wks	mean 15.3% (±9.7)* median 15.0% (3-30)†	mean 12.9% (±10.4)* median 10.0% (0.5-30)†	p=0.41

* Standard deviation; † 5th - 95th percentile; N/A: not applicable

case of such a consultation, 56% answered they would give basic information. Seven percent would give detailed information, whereas 37% would give no information and refer to a gynecologist directly. Considering that over 60% of midwives would give at least some information, it is remarkable to note that only 2% of all patients had heard of progesterone treatment through their midwife. These numbers further support the observation that progesterone treatment to prevent recurrent preterm birth is a largely unknown strategy among midwives.

It should be noted here that in the Dutch system, obstetric care is provided to low-risk women by midwives only, whereas gynecologists are involved in the care for high-risk pregnancies. A formal list of obstetric referral indications, which is composed by obstetricians and midwives together, states that a previous spontaneous preterm birth that occurred before 33 weeks of gestation is an indication for referral.[10] However, when a term pregnancy has taken place after the preterm birth, the indication is canceled. Moreover, unfamiliarity with the potential effectiveness of progesterone might, in absence of other effective treatments, be a cause of nonreferral to gynecologists. Better education and information of midwives on this subject may help to clear away this barrier.

As with midwives, unfamiliarity with treatment options was the most noticeable finding in the patient questionnaire. Treatment was known in only 27% of patients. Another issue that needs to be addressed is the uncertainty among patients with regard to the safety of progesterone treatment.

The motive for the current study arose during the registration of patients treated with progesterone between 2004 and 2006. The Dutch Society for Obstetrics and Gynecology (NVOG) had not issued a guideline on the prevention of recurrent preterm birth until March 2007. Of note, however, all surveys in this study were conducted after April 1, 2007, and knowledge of the guideline was therefore measured to a certain extent, albeit not fully intentionally.

A 2005 survey conducted among board-certified maternal-fetal medicine specialists in the United States showed that 67% of respondents were using progesterone in clinical practice. In our study, this was only 25%.[11] This may in part be due to a slower dissemination process of evidence that has been produced abroad. In comparison, progesterone use among maternal-fetal medicine specialists in late 2003, shortly after the publication of the trials by Meis et al and Da Fonseca et al, was only 38%.[12]

Evidence-based treatments are not self-implementing.[13] Studies suggest that, in addition to publication and dissemination of guidelines, more intensive intervention strategies are necessary to promote implementation of evidence.[14-16] It is increasingly recognized that these intervention strategies should be based upon assessment of potential barriers, as we did in the present study.

In the Netherlands, national guidelines generally leave some room for interpretation, which causes a variation in local protocols throughout the country. In certain regions, however, arrangements have been made so as to attune local management to facilitate

Table 3 Factors determining patients' willingness to undergo treatment with progesterone to prevent recurrent preterm birth

	Willing to use progesterone (n=53)	Unwilling to use progesterone (n=46)
General characteristics		
Previous awareness of progesterone treatment	20 (74%)	7 (26%)
Age		
26-30 yrs	19 (56%)	15 (44%)
≤25 yrs	7 (64%)	4 (36%)
31-35	18 (56%)	14 (44%)
≥36 yrs	9 (41%)	13 (59%)
Level of education: high school or higher	46 (61%)	30 (39%)
Ethnicity: white/Caucasian	42 (54%)	36 (46%)
Obstetric History		
2 or more previous preterm births	11 (69%)	5 (31%)
1 or more previous term births	5 (31%)	11 (69%)
1 or more deceased children	13 (65%)	7 (35%)
GA most severe preterm birth	mean 27.6 (±4.0)* median 28.0 (19.1-32.3)†	mean 29.4 (±3.9)* median 30.5 (20.0-33.7)†
GA of most recent preterm birth	mean 28.6 (±3.0)* median 29.5 (24.0-32.3)†	mean 30.2 (±2.8)* median 31.0 (26.0-34.0)†
Neonatal outcome of most recent preterm birth		
MC admittance	4 (33%)	8 (67%)
NICU admittance	46 (57%)	35 (43%)
Deceased within 24 hours	3 (50%)	3 (50%)
Length of stay on NICU most recently preterm born child	mean 34.3 (±33.8)* median 20.0 (0-100.8)†	mean 24.6 (±26.6)* median 14.5 (0-77.0)†
Current condition most recently preterm born child		
Healthy	45 (51%)	43 (49%)
Moderately handicapped	1 (100%)	0
Deceased	7 (70%)	3 (30%)
Knowledge of preterm birth		
Estimated incidence of preterm birth	mean 20.7% (±17.5)* median 15.0% (3.6-75.0)†	mean 23.3% (±20.2)* median 15.0% (5.0-77.8)†
Estimated incidence mortality	mean 14.1% (±14.4)* median 8.0% (1.0-52.0)†	mean 13.0% (±14.0)* median 6.0% (0.7-48.5)†
Estimated incidence handicaps at age 10	mean 27.3% (±18.0)* median 25.0% (3.1-62.3)†	mean 26.7% (±19.1)* median 25.0% (2.2-68.0)†
Estimated recurrence risk	mean 31.9% (±17.4)* median 33.3% (3.4-64.5)†	mean 33.3% (±19.2)* median 30.0% (5.0-78.9)†
Attitude towards treatment		
Belief in treatment safety for child	15 (83%)	3 (17%)
Belief in treatment safety for mother	22 (76%)	7 (24%)
Discomfort expected from treatment on scale 1-5		
intramuscular injections	mean 2.7% (±1.2)* median 3.0% (1-5)†	mean 3.1% (±1.3)* median 3.0% (1-5)†
weekly visits to hospital or GP	mean 2.6% (±1.2)* median 3.0% (1-5)†	mean 2.7% (±1.4)* median 3.0% (1-5)†
possible direct side effects	mean 2.8% (±1.3)* median 3.0% (1-5)†	mean 3.5% (±1.2)* median 4.0% (1-5)†

* Standard deviation; † 5th - 95th percentile; GA: gestational age; N/A: not applicable

	Univariate analysis Odds Ratio (95% CI)/p-value	Multivariate analysis Odds Ratio (95% CI)
	3.4 (1.3 to 9.0)	1.9 (0.63 to 5.9)
	1.0 1.4 (0.34 to 5.6) 1.0 (0.38 to 2.7) 0.55 (0.18 to 1.6)	
	3.5 (1.3 to 9.3)	4.7 (1.2 to 18.8)
	1.1 (0.41 to 2.7)	
	2.1 (0.71 to 6.4)	
	0.33 (0.11 to 1.0)	
	1.8 (0.67 to 4.9)	
	p=0.033	1.1 (0.9 to 1.3)
	p=0.007	0.74 (0.57 to 0.96)
	1.0 2.6 (0.73 to 9.4) 2.0 (0.27 to 14.8)	
	p=0.115	
	0.39 (0.11 to 1.5) n/a 2.2 (0.57 to 8.2)	
	p=0.504	
	p=0.705	
	p=0.889	
	p=0.706	
	5.4 (1.5 to 18.9)	3.8 (0.6 to 23.7)
	3.8 (1.5 to 10.0)	1.6 (0.37 to 6.5)
	p=0.108 p=0.688 p=0.015	0.7 (0.46 to 1.06)

referral between different hospitals and more particularly referral to academic centers. In our opinion, implementation of new treatments in nonacademic and nonteaching hospitals is best reached through these regional clusters.

As earlier studies have shown, guidelines can be disseminated effectively through opinion leaders in the field.[17] At present, a plan is being formed by several gynecologists in collaboration with Dutch government health organizations, where both an obstetrician and a neonatologist from an academic hospital visit all non-academic hospitals in their referral circle to discuss perinatal management. Each hospital is to be visited twice yearly, and during these meetings protocol content will be an important item. Thus, new developments that are generally more quickly observed by academic centers will be implemented throughout the rest of the country more rapidly.

Classic ways of education such as lectures and written materials may aid in achieving implementation, but further measures are needed. In this study, 70% of patients who were aware of progesterone treatment were willing to try this in a future pregnancy versus 46% of patients who were previously unaware. Patients with previously existing knowledge had received information from their gynecologist in 82% of cases. It is likely that willingness to use progesterone at the doctor level will translate directly to patient level. To improve implementation in gynecologists, dissemination of knowledge by academic opinion leaders on a regional level will probably be the most effective approach.

Conclusion

In view of the results of the questionnaire, we conclude that most ground can be won in implementation of progesterone treatment for the prevention of recurrent preterm birth when this strategy is included in local protocols, thereby expressing toward gynecologists the support of the clinic and opinion leaders in the field. Focus of implementation should be mainly on gynecologists in nonacademic and more specifically nonteaching hospitals.

Acknowledgements

We thank all gynecologists, midwives, and patients who have participated in the questionnaire.

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