Chapter 11

Patient's preferences for screening and treatment with progesterone in relation to preterm birth

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Abstract

Objective: To explore pregnant women's preferences regarding cervical length measurement by ultrasound and treatment with progesterone in relation to preterm birth prevention.

Study Design: Discrete choice experiment.
Four hospitals, four ultrasound centres and ten midwifery practices spread over the country have been contacted to distribute at least 10 questionnaires among pregnant women between 15-36 weeks of gestation.
Of the 156 questionnaires that were actually handed out, 138 were returned.

Methods: Each questionnaire existed of 16 choice sets with two screening/treatment options and one 'no screening/treatment' option. The options consisted of 1) transvaginal or abdominal cervical length measurement, 2) vaginal or oral administration of progesterone, 3) short-term health risk and 4) long-term health risk for the child. The relative importance of the choices and trade-offs patients were willing to make were analysed with mixed logit regression in STATA.

Mean outcome measure: Most respondents made trade-offs between attributes and all screening/treatment characteristics proved important in their decision making.

Results: Transvaginal cervical length measurements were not preferred (p=0.01) and was traded only in exchange for an absolute decrease of 6.5% (95% CI 2.6 – 10.4) in long-term neonatal complication rate. Previous experience with adverse neonatal outcome affected the preferences of the women.

Conclusion: Low risk women in The Netherlands are prepared to undergo screening for preterm birth if this strategy reduces the long-term neonatal complication rate with at least 6.5%.

Introduction

Since preterm birth is the main contributor to perinatal mortality and morbidity, the focus of many studies is on the risk assessment on preterm birth[1-3]. Pregnant women with a short cervical length, measured either with abdominal or transvaginal ultrasound, are at increased risk of having a preterm birth[4-7]. Vaginal progesterone administration during pregnancy can potentially decrease the number of preterm births and lower neonatal mortality and morbidity[8-11]. In this context the Dutch Obstetric Consortium performed a nationwide cohort study on screening women with a singleton pregnancy for short cervical length, under the acronym 'Triple P' ({HYPERLINK"http://www.studies-obsgyn.nl "})[12]. This acronym is an abbreviation formed of the initial P's in 'Preventing Preterm birth with Progesterone'. Women with cervical length ≤ 30 mm were invited to participate in the embedded randomised clinical trial to receive either vaginal progesterone or placebo capsules until 34 weeks.

The Triple P study started in December 2009. The power calculation dictated a sample size of 1920 participants per arm to prove or refute a 50% reduction of preterm birth (from 5% to 2.5%) after treatment with progesterone. During the study period, we noticed that considerably less pregnant women than we anticipated were willing to give informed consent and declined cervical length measurement. Moreover, to our surprise, even if the cervical length was measured ≤ 30 mm, which meant a considerable high risk on preterm birth, quite a few (27.5%, N103/375) women refused a second cervical length measurement or did not consent to randomization (47%, N71/151). Insight in patient's thoughts regarding the risk of preterm birth and the health impact of their child, compared to the intervention (i.e. vaginal progesterone), is therefore of utmost importance.

A quantitative approach to measure preferences, which is increasingly used in health care, is a discrete choice experiment. This is a formal methodology to evaluate respondents' preferences to explore trade-offs that patients make between different treatment alternatives. Within a discrete choice experience respondents are asked to choose between two or more alternative's or treatment options. Discrete choice experiments have become more common and useful to investigate acceptability of interventions before general introduction[13-15].

Understanding the considerations in pregnant women in expressing their preferences, can contribute to improvement in patient counselling. We choose a discrete choice experiment to value trade–offs between management options

in relation to preterm birth, i.e. cervical length measurement and progesterone administration, versus health outcome of the new born child as a consequence of preterm birth.

Materials and methods

Setting

This patient's preference study was conducted alongside the Triple P study[12], a multicentre cohort study (Triple P screening) with a subsequent randomised clinical trial (Triple P treat) performed by the Dutch Obstetric Consortium ({HYPERLINK" http://www.studies-obsgyn.nl/TripleP "}). The Dutch Consortium is a collaborative research network of university and general hospitals in The Netherlands. In the Triple P study 23 general and seven university hospitals participated, along with approximately 160 primary care midwifery practices and 29 ultrasound centres. At the time of the patient's preference study, the Triple P continued for another year.

Participants

Mid- 2012 four hospitals, four ultrasound centres and ten midwifery practices spread across the country, were asked to distribute at least ten discrete choice experiment questionnaires among pregnant women between 16-36 weeks of gestation. Only pregnant women who had been informed about the Triple P study and who were willing to undergo or already had taken part in the standard anomaly scan at 18-22 weeks of gestation could participate. Participation was voluntary. The institutional review board of the Academic Medical Centre was informed about this study and exempted the study from IRB approval. One hundred and ninety questionnaires were sent to the participating hospitals, ultrasound centres and midwifery practices. The only condition to fill in the questionnaire was sufficient understanding of the Dutch language.

Questionnaire

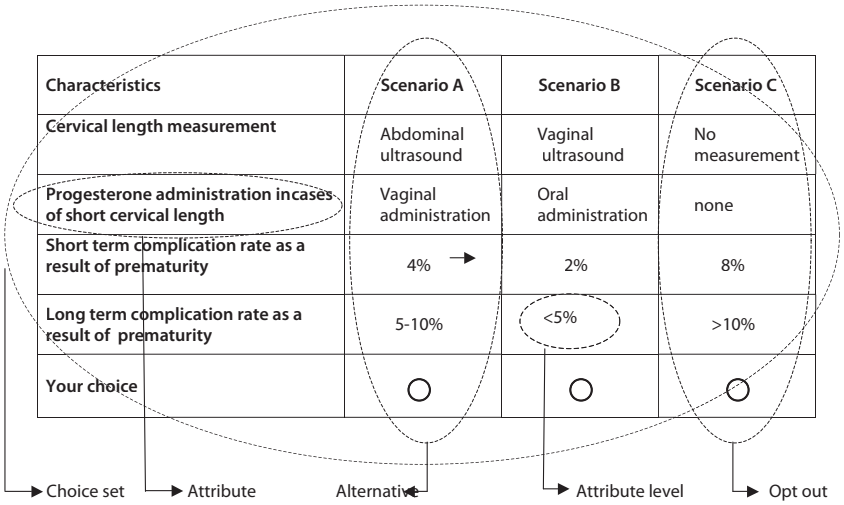
The introduction section of the questionnaire consisted of explaining the purpose of the study as well as general information on preterm birth consequences, cervical length measurement and treatment with progesterone. In the explanation about cervical length measurement, vaginal ultrasound was mentioned as the most accurate and therefore the most preferable technique of cervical length

measurement, especially in case of short cervix. Also, information was given regarding the administration of progesterone (oral or vaginal) and about the safety of progesterone application during pregnancy. No difference was mentioned in the efficacy of the administration. The relation between gestational age at delivery and admission to neonatal ward as a result of prematurity was also discussed, i.e. a poorer outcome is to be expected with decreasing gestational age.
Besides the introduction, the questionnaire consisted of two parts. In the first part general data about the women were collected. This included maternal age, native country, experience with prior vaginal examination, obstetric history, treatment of perinatal complications of previous born children, participation in the standard anomaly scan and obstetric care provider (primary- or secondary care). In the second part preferences for cervical length measurement, treatment with progesterone and preterm birth complications were studied by means of discrete choice experiment. At the end of the questionnaire respondents were asked to indicate the difficulty of the questionnaire on a scale of 1 to 10, in which 1 was very difficult and 10 very easy.

Discrete choice experiment

The technique of discrete choice experiment is based on the assumption that health-care interventions (or treatments) can be described by their characteristics. A discrete choice experiment investigates which trade-offs patients are willing to make between risks and benefits of a certain treatment option. Figure 1 illustrates the concept of this discrete choice experiment and its definitions. The characteristics or so called 'attributes', consisted of treatment options and risks, and are described in the first column. Scenario A and B describe the possibility of choosing a treatment with varying health risks. Scenario C, the opt out, can be selected if the respondent prefers no optioned treatment. The risk outcome in the opt-out scenario was always equal to or worse than in the other scenario's.

Figure 1: Example of choice set as presented in the questionnaire



The respondents were asked to make a choice between two or more sets of hypothetical alternatives with systematically varying combinations of attribute levels.[15] The importance of the attributes can be estimated by analysing the choices the responders made between attributes and attribute levels.

Attribute and attribute levels

The selection of the attributes and levels was based on data from literature on prevalence of preterm birth and short- and long-term impact of prematurity[16-24]. After discussing the short and long-term risk levels in the expert group, these were converted into understandable explanations and risk levels for respondents. From the literature it is known that in discrete choice experiment studies 4-6 attributes is most common and that most studies use 9-16 choices[25,26]. The greater the number of attributes, the more difficult it is to complete a discrete choice experiment. A completion time between 10-15 minutes seemed mostly acceptable[25]. Potential attributes and levels were discussed with specialists on discrete choice experiment development as well as with obstetric care providers and paediatricians. After consensus on the attributes and levels by both expert groups, the questionnaire was presented to two midwives and four pregnant women to test whether the questionnaires were comprehensible. After that, no changes were made.

Four attributes were selected: cervical length measurement, treatment with progesterone and short- and long-term preterm birth complications (figure 1) with three levels per attribute. Attributes and corresponding levels are shown in table 1.

Table 1: Attributes with corresponding levels

Attributes	Levels
cervical length measurement	none
	abdominal ultrasound
	vaginal ultrasound
progesterone administration	none
	oral administration
	vaginal administration
risk of short term health care problems due to prematurity	2%
	4%
	8%
risk of long term health care problems due to prematurity	<5%
	5-10%
	>10%

Short term health care problems due to prematurity were defined as temporarily neonatal hospitalization for instance because of respiratory problems, glucose fluctuations, temperature- or nutritional problems or jaundice. Long term health care problems due to prematurity were defined as complications requiring permanent care and attention, not only during the period of hospitalization. This included developmental delay, learning- or behavioural problems, impaired concentration, vision- or hearing problems and spasticity. Both short and long-term problems were transformed into attributes as complication rates due to prematurity.

Respondents had to choose their most preferable option in each choice set. Every choice set included one no treatment (opt-out) option. This opt-out was necessary since, as in real life, respondents are not obliged to take a treatment. Thus the women were asked to choose in each choice set between three hypothetical alternatives, two screening/treatment options differing in 1) vaginal or abdominal cervical length measurement, 2) vaginal or oral administration of progesterone, 3) short-term health risk and 4) long-term health risk for the new born child, and one 'no screening/treatment' opt out option.

Development of choice sets

The combination of four attributes and three levels per attribute provided 81 (3^4) hypothetical alternatives. The alternatives were placed into balanced choice sets with a minimum overlap. We used a fractional factorial design to generate a functional sample of 16 alternatives. The fractional factorial method systematically selects this sample according to an orthogonal design. Orthogonality guarantees an optimal balance of the attribute levels with zero correlation between the attributes[27,28]. The orthogonal design was generated by Orthoplan (Statistical Package for Social Sciences [SPSS] version 16 SPSS Inc., USA).

The 16 alternatives formed 'treatment A' in each of the 16 choice sets. To ensure minimal overlap of attribute levels, we created a set of alternatives to form 'treatment B' by means of a syntactical fold over technique, based on the profiles of 'treatment A' [15]. This resulted in 16 different choice sets, whereby each choice set consists of two alternatives representing hypothetical risks and treatment options in relation to preterm birth. A not changing opt-out or no treatment option was added as a third alternative. The health care consequences in this no screening/treatment alternative were either equal or worse than one of the other screening/treatment alternatives. The 16 choice sets for screening/treatment option A and B, and C (opt-out) were considered sufficient to estimate all main effects representing the relative importance of each attribute or attribute level. To assess the understanding of the attributes (treatment options and risk effects), the questionnaire contained one dominant question in which all attributes were in favour of one specific choice. This is called a rationality test.

Analyses

A mixed logit regression model for panel data was employed to analyse the effect of the attribute levels on women's preferences in STATA 12.1[29]. Each discrete choice experiment attribute was included in the regression model. The 'no treatment' alternative was included as an alternative specific constant to account for any latent or uncontrolled factors when choosing the 'no treatment' alternative.

Short-term and long-term complication rates were coded as continuous variables after testing for linearity. As cervical length measurement and the progesterone administration in case of short cervix are categorical variables, these were recoded as -1, 0 and 1 (effects coding).

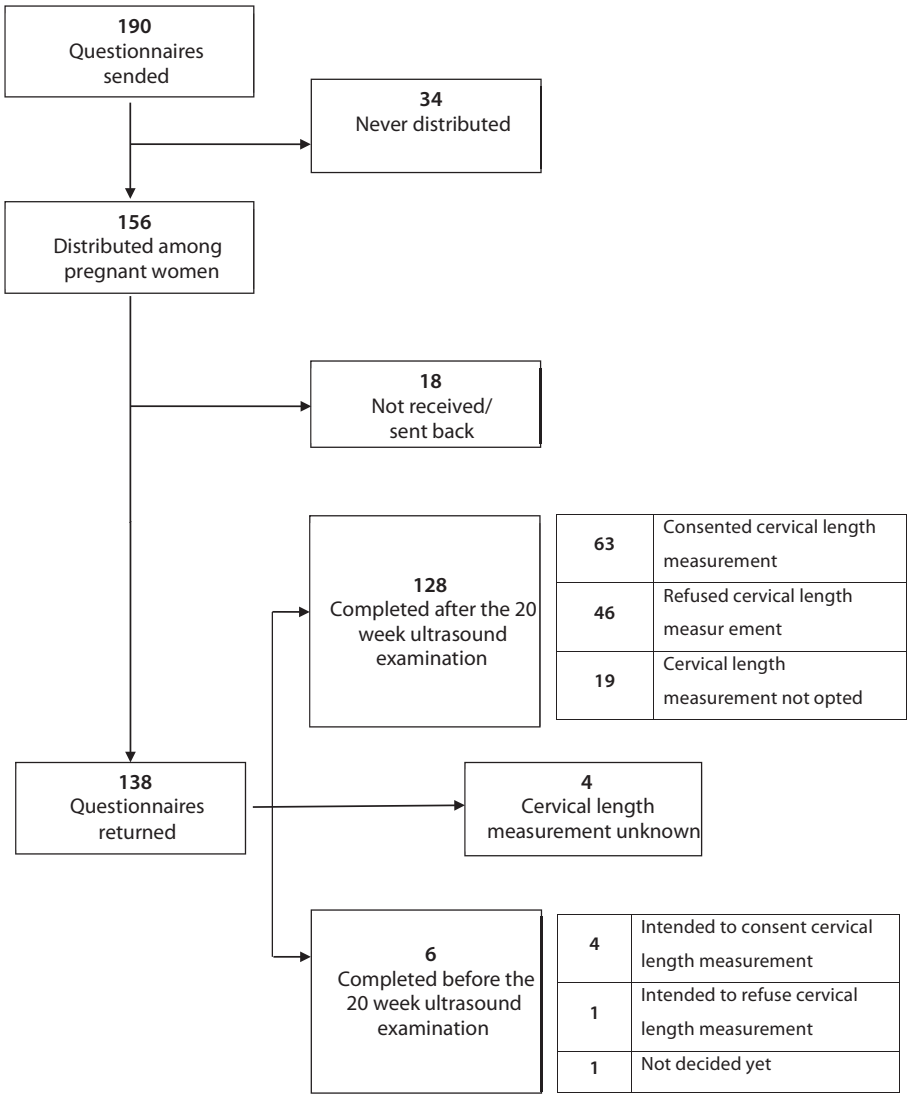
The constant of the model was set as a random parameter. Subsequently random parameters for attributes were included based on the model fit (AIC and Chi-square

tests). A normal distribution was assumed. The statistical significance of a coefficient (p-value ≤ 0.05) indicates that individuals differentiated between one attribute (or attribute level) and another in making stated choices. The sign of a coefficient reflects whether the attribute has a positive or negative effect on preference score. The value indicates the relative importance of the attribute to total relative utility. A statistically significant coefficient indicates that respondents considered that attribute important. We expected that the attributes short- and long-term risks would have a negative effect to reflect the preference for low risks/complications. If long-term risk would be valued as more important than short –term risk then this would be reflected in a higher negative preference value.
Trade-offs that respondents are willing to make between attributes were estimated by calculating the ratios of the coefficients of two attributes where we also accounted for preference heterogeneity. As both the constant and the expected outcome attributes were included as random parameters in the analyses, the trade-offs could not be calculated directly. We calculated importance scores to visualize the relative importance of a given attribute by dividing the difference in utility between highest and lowest level for a single attribute by the sum of the differences of all attributes. A simulation (n=1000) was used to estimate the trade-offs. A sensitivity analysis was done excluding women that failed the rationality test. Subgroup analyses were conducted using two-way interaction terms in the regression model to assess the effect of specific baseline parameters. In case of a significant interaction results are presented sub grouped for that term.

Results

In May 2012 190 questionnaires were sent to the participating hospitals (4), ultrasound centres (4) and midwifery practices (10) to be distributed to the pregnant women who are under their control. In November 2012 actually 156 of the 190 the questionnaires were handed out, and 138 were returned, resulting in a response rate of 88%. In total 128 respondents filled in the questionnaire after the 20-week ultrasound examination was completed, six women before the 20-week ultrasound examination was performed and four of the respondents had not filled in whether their cervical length was measured or not. Figure 2 shows the flowchart of the 190 questionnaires.

Figure 2: Flowchart of the distributed questionnaires



One questionnaire was excluded from the analysis as none of the discrete choice experiment questions were answered. All other 137 questionnaires were fully completed with only some exceptions in the general information section, i.e. once postal code was missing, once date of birth, once date of completion and twice gravidity. The baseline characteristics of the respondents are shown in table 2.

Table 2: Baseline characteristics of the 138 respondents

Baseline characteristics	N=138
Age in years, mean (SD)	31 (4.3)
Native country, N (%)	
Netherlands	130 (94.2)
Other	8 (5.8)
Gravidity N (%)	
First pregnancy	60 (43.5)
Second pregnancy or more	76 (55.1)
Gestational age(weeks), mean (SD)	23 (3.9)
Gestational age at time responding N (%)	
Before anomaly scan	8 (5.8)
After anomaly scan and < 32 weeks gest.	121 (87.7)
≥ 32 weeks of gestation	7 (5.1)
Previous vaginal examination N (%)	
No previous vaginal examination	26 (20.3)
Discomfort/pain during previous examination	30 (21.7)
Cervical length measurement N (%)	
Agreed	65 (47.1)
Refused	49 (35.5)
Unknown/ not offered	24 (17.4)
Previous child needed extra care, N (%)	12 (8.7)
Antenatal care provider, N (%)	
Primary care midwife	104 (75.4)
Obstetrician in secondary/tertiary care	28 (20.3)
Other/ unknown	6 (4.3)

The dominant question- in which the most favourable outcome was related to the least interventions, -treatment and complication rates- was answered as expected by 132 women (97%), only five women did not provide the expected answer. The opt-out / no treatment option was chosen in 21% of the choice sets. Ten women opted for the 'no treatment' choice at all 16 questions, i.e. these women did not want to trade-off their choice. These 10 women did neither opt for cervical length measurement nor for progesterone administration. The questionnaire was difficult to answer for 41 (30%) women, who scored the difficulty as 5 or lower on a scale of 1 to 10. Still, there was no difference between the choices these women made and those of the women who found the questionnaire not difficult. Seventy six women (56%) scored the questionnaire as easy with a score of 7 or higher. Five respondents did not answer this question.

Table 3 shows the results of the regression model, which contains the main effects of the attributes.

Table 3. Four attributes were used for discrete choice experiment to assess women's preferences. The negative sign of the coefficient reflects a negative effect on utility, the value indicates the relative importance of the attribute to total relative utility. A statistically significant coefficient indicates that respondents considered that attribute important.

Attribute levels **Attributes and levels**	**Mean coefficient (95%CI)**	**Standard deviation (95%CI)**
Constant[#]	3.65 (1.41 to 5.89)*	1.56 (0.34 to 2.78)*
Cervix length measurement		
No measurement (omitted)	1.64 (1.10 to 2.18)*	1.69 (0.29 to 3.19)*
Abdominal	*-0.77 (-1.03 to -0.51)**	0.38 (-0.03 to 0.79)
Vaginal	*-0.87 (-1.39 to -0.35)**	0.63 (0.05 to 1.21)*
Progesterone administration		
No (omitted)	0.71 (0.63 to 0.99)	0.21 (0.03 to 0.39)*
Oral	*-0.21 (-0.26 to -0.16)**	0.05 (0.00 to 0.09)
Vaginal	*-0.49 (-0.70 to -0.28)**	0.12 (0.01 to 0.23)*
Short-term complication rate (per 1%)	*-0.16 (-0.24 to -0.08)**	0.04 (-0.06 to 0.15)
Long-term complication rate (per 1%)	*-0.37 (-0.55 to -0.19)**	0.12 (-0.05 to 0.29)
Number of responses	6624	
Number of respondents	138	
Log likelihood	-874	
AIC	91	
BIC	97	

[#]Alternative specific constant for no treatment (the opt-out) *P<0.01

All coefficients were statistically significant in all cases on the choice-making of respondents. The mean coefficient indicates the relative likelihood of choosing a treatment alternative with a given attribute-level combination holding all other factors constant. A larger value indicates a greater likelihood of choosing a treatment alternative with the specific feature. No cervical length measurement was preferred above a cervical length measurement by abdominal ultrasound examination (mean coefficient -0.77 vs 1.69; p<0.01) or vaginal ultrasound (mean coefficient -0.87 vs 1.69; p<0.01). No progesterone administration was preferred above oral (mean coefficient -0.21 vs 0.71; p<0.01) and vaginal progesterone (mean coefficient -0.49 vs 0.71; p<0.01). Oral progesterone was preferred above vaginal progesterone (mean coefficient -0.21 vs -0.49; p<0.05). The standard deviation of the mean coefficient describes the degree to which respondent preferences were heterogeneous. As can be seen from table 3 most estimated standard deviations were significant. Larger values indicate more heterogeneity across respondents. For example, from the results it can be inferred that no CL measurement had the greatest preference heterogeneity with an estimated standard deviation of

1.69. This indicates that although most respondents preferred no cervical length measurement (mean preference = 1.64) a part of the participants actually did prefer a cervical length measurement. The sensitivity analysis, excluding the five women that did not correctly answer the dominant question, did not influence the main effects of the model.

Willingness to trade preferences

Most respondents were willing to make trade-offs between attributes. No cervical length measurement would be traded for a vaginal cervical length measurement in exchange for a 6.5% (95% CI 2.6 to 10.4) decrease in long-term complication rate. Similarly, no progesterone administration would be traded for vaginal progesterone administration in exchange for a 7.3% (95% CI 5.1 to 9.6) decrease in short-term complications risk.

Effect of baseline parameters

In a secondary analysis we evaluated the effect of baseline parameters on the choices of the participating women. Of the baseline parameters only women who previously had a new born child that needed extra care was a significant interaction term. Women who previously had a new born child that needed extra care made different choices; these women preferred the use of a vaginal cervical length measurement while means of progesterone application was not an important attribute for this group of women. As only 12 women had a previous new-born that had needed extra care (for instance because of asphyxia, hypothermia, hypoglycaemia, small- or large for gestational age, jaundice, infection etc.) the power of this sub analysis was very low. The sub analysis stratified for women who did and who did not previously had a new born child that needed extra care is shown in table 4.

Table 4: Results of the sub analysis stratified for women who did and who did not previously had a new born child that needed extra care

Attributes and levels	Previous delivery requiring extra neonatal care		No extra neonatal care previous delivery	
	Mean coefficient (95% CI)	SD (95% CI)	Mean coefficient (95% CI)	SD (95% CI)
Constant	2.87 (0.65 to 5.09)*	0.35 (0.01 to 0.69)	0.05 (-0.11 to 0.22)*	1.03 (0.04 to 2.02)*
Cervix length measurement				
No measurement (omitted)	-1.77 (-2.85 to -0.65)*	0.81 (-0.07 to 1.69)	1.57 (1.05 to 2.09)*	1.14 (1.01 to 1.27)*
Abdominal	0.65 (-0.13 to 1.43)	0.45 (0.01 to 0.89)*	-0.68 (-0.93 to -0.43)*	0.25 (0.06 to 34)*
Vaginal	1.12 (0.02 to 2.22)*	0.58 (-0.16 to 1.32)	-0.89 (-1.31 to -0.47)*	0.72 (0.02 to 1.42)*
Progesterone administration				
No (omitted)	0.02 (-0.01 to 0.05)	0.13 (-0.09 to 0.35)	1.17 (0.98 to 1.36)	0.71 (0.17 to 1.24)
Oral	–0.21 (-0.43 to 0.01)	0.25 (-0.02 to 0.52)	-0.52 (-0.67 to -0.37)	0.09 (-0.03 to 0.12)
Vaginal	0.22 (0.03 to 0.41)*	0.20 (-.11 to 0.51)	-0.65 (-0.84 to -0.46)	0.52 (0.03 to 1.01)*
Short-term complication rate (1%)	-0.16 (-0.31 to -0.01)	0.02 (-0.03 to 0.07)	-0.17 (-0.31 to -0.03)	0.07 (-0.09 to 0.23)
Long-term complication rate (1%)	-0.43 (-0.73 to -0.13)	0.04 (-0.07 to 0.15)	0.37 (-0.58 to -0.16)	0.09 (-0.11 to 0.39)
Log likelihood	-564		-564	

*p<0.05

Discussion

Mean findings

We evaluated women's preference for cervical length measurement and progesterone administration in relation to health problems of their new born child due to prematurity. The participating low risk women generally expressed a preference for least interventions and least side effects but were willing to make trade-offs between attributes when this resulted in better health outcomes for their child. A cervical length measurement and progesterone administration were not preferred. However a transvaginal ultrasound cervical length measurement was accepted in exchange for a 6.5% decrease in long-term neonatal complication rate. Opposite to the general population, the subgroup of women who experienced adverse neonatal outcome did have a preference for transvaginal ultrasound cervical length measurement. Due to their experience, these women are more likely to be fully aware of the risk of preterm birth. It must be stressed however that the power for this sub analysis was limited due to the low number of respondents (8.8%, 12/137) who experience adverse neonatal outcomes. Although the numbers in the subgroup analysis were small, this confirms clinical experience that women with a previous adverse outcome, will try to avoid a repetition of that adverse outcome.

Strengths and limitations

Our study provides insight into the relative weight women place on risk selection and health outcome of preterm birth and trade-offs they make. As far as we know this is the first discrete choice experiment in relation to risk selection and health outcome due to prematurity.

A limitation of our study may be that the participating women did not fully understand the questions and/or presented risks. It is known from literature that individuals have difficulty in understanding risk assessment[30,31]. Risk communication in complication rates may be hard to understand and therefore respondents may have had different perceptions towards risk problems due to prematurity. In an effort not to make the choice sets unnecessarily complicated, we opted to describe the risk assessment as a result of prematurity as short and long term complications (with additional information in the introduction section of the questionnaire). So, we decided not to make a further distinction according to gestational age at birth. Nevertheless, although the majority of the participating women reported

that the questionnaire was easy to understand, 30% of the women reported the questionnaire to be difficult (score 5 or lower). Still, the choices these women made did not seem different from the choices the women made that judged the questionnaire to be easy. Furthermore, the dominant control questions were answered correctly by 97% of the women. It seems therefore that the difficulty of the questionnaire did not have a major effect on the validity of the results.
Several models are available to analyse discrete choice data[14]. A mixed logit model or a latent class model were both good alternatives to analyse the choice observations in the present discrete choice experiment. Testing the basic model using a latent class model with three knots resulted in a comparable AIC, making it unlikely that a latent class model would have resulted in different estimates.

Interpretation

The best hope for reducing the incidence of preterm birth at present seems to be screening followed by treatment of women at risk. Therefore it is important to have as much information as possible about women's attitudes regarding this approach. Ongoing the triple P study, it was noticed that considerably less pregnant women were willing to measure their cervical length than expected. Moreover, even if the cervical length was measured ≤ 30 mm, quite a few women refused the second measurement or did not consent to randomization. It seemed that women do not want to think about future pregnancy risks or, if they do, seem to believe that it will not happen to them. Another explanation could be a lack of awareness of the complications as a result of (even late) preterm birth in pregnant women. This seems to be confirmed by the study of Goldenberg *et al.*[32] who reported that half of 650 surveyed women believed it is safe to deliver before 37 weeks of gestation. Nevertheless, the present study shows that most women were willing to trade-off their first choice. Moreover, women with previous adverse neonatal outcomes make different choices and preferred the use of a transvaginal cervical length measurement, thus confirming our hypothesis that the given information about the consequences and the prevention of preterm birth are essential to make a trade off . It therefore appears, that better counselling (or even face-to-face information) and sharing parents experiences is crucial in increasing awareness of pregnant women of the risks of preterm birth and the possibility to prevent preterm birth. In this way we assume that women will undergo the required interventions in future.

Conclusion

This study shows that women at low risk for preterm birth generally expressed a preference for least interventions but were willing to make trade-offs between attributes when this resulted in better health outcomes for their child. The results of this study can be used to improve the counselling for the prevention of preterm birth in pregnant women and to achieve an enhanced participation in screening and treatment programs to prevent preterm birth.

Statement of contribution

AV, MW wrote the first draft of the paper. MW analyzed the data. AV, LW, MH, and EB conceived the study. MO, BK, CG, EP, BM critically revised the manuscript for important intellectual content. All authors approved of the final version of the manuscript to be submitted.

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