

Amniocentesis for PPRM Management: A Feasibility Study

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Abstract

Objective: In Canada, most mothers whose amniotic membranes rupture before 34 weeks' gestation are hospitalized and delivered when signs of chorioamnionitis or fetal distress are observed or when a predetermined gestational age between 34 and 37 weeks is reached. This management approach can be questioned because in utero exposure to infection is a risk factor for cerebral palsy in neonates. Amniocentesis has the potential to detect markers of intra-amniotic infection. Our objective was to determine the acceptability of a randomized study comparing expectant management with amniocentesis-based management in women with premature rupture of the membranes.

Methods: Between November 2005 and January 2007, we conducted a qualitative study involving 40 patients admitted to a tertiary care centre with premature rupture of the membranes between 28 and 34 weeks. The participants read an information booklet and answered a questionnaire. They were asked if they would agree to participate in a randomized study comparing expectant management with amniocentesis-based management. They graded the importance of a series of statements in their decision-making process.

Results: Seventy percent (28/40) of patients would have participated in the proposed study. Determining the presence of amniotic fluid infection or lung maturity was the main reason motivating their choice. The reasons for refusing to participate were related to complications of amniocentesis (fetal trauma, iatrogenic preterm labour, infection, or pain).

Conclusion: The majority of patients with premature rupture of the membranes would participate in a study comparing expectant management to management based on amniocentesis results. This study helped us to better understand their motivations and fears.

être remise en question puisque l'exposition *in utero* à l'infection constitue un facteur de risque d'infirmité motrice cérébrale chez les nouveau-nés. L'amniocentèse présente le potentiel de détecter les marqueurs de l'infection intra-amniotique. Notre objectif était de déterminer l'acceptabilité d'une étude randomisée comparant la prise en charge non interventionniste à la prise en charge fondée sur l'amniocentèse chez les femmes connaissant une rupture prématurée des membranes.

Méthodes : Entre novembre 2005 et janvier 2007, nous avons mené une étude qualitative portant sur 40 patientes admises à un centre de soins tertiaires et qui connaissaient une rupture prématurée des membranes entre la 28^e et la 34^e semaine de gestation. Les participantes ont lu une brochure d'information et ont rempli un questionnaire. On leur a demandé leur opinion quant à la participation à une étude randomisée comparant la prise en charge non interventionniste à la prise en charge fondée sur l'amniocentèse. Elles ont classé, en ordre d'importance, une série d'énoncés liés à leur processus de prise de décision.

Résultats : Soixante-dix pour cent (28/40) des patientes auraient participé à l'étude proposée. La détermination de la maturité pulmonaire ou de la présence d'une infection du liquide amniotique constituait la principale raison expliquant leur choix. Les raisons motivant le refus de participer étaient liées aux complications de l'amniocentèse (traumatisme foetal, travail préterme iatrogène, infection ou douleur).

Conclusion : La plupart des patientes connaissant une rupture prématurée des membranes participeraient à une étude comparant la prise en charge non interventionniste à la prise en charge fondée sur l'amniocentèse. Cette étude nous a aidés à mieux comprendre leurs motivations et leurs peurs.

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Résumé

Objectif : Au Canada, la plupart des mères dont les membranes amniotiques se rompent avant la 34^e semaine de gestation sont hospitalisées; de plus, leur accouchement est déclenché lorsque l'on constate des symptômes de chorioamnionite ou de souffrance foetale, ou lorsqu'un âge gestationnel prédéterminé (entre 34 et 37 semaines) est atteint. Cette approche de prise en charge peut

INTRODUCTION

Preterm premature rupture of the membranes complicates 3% of pregnancies and is responsible for approximately one third of all preterm births.^{1,2} PPRM is an important cause of perinatal morbidity and mortality because it is associated with chorioamnionitis, placental abruption, and neonatal sepsis.²⁻⁵ While expectant management with antibiotics and steroids has been favoured in the past, preferred management in women with PPRM is the centre of a major debate. Moreover, it is likely that optimal management will differ according to gestational age at the time of PPRM.

Key words: Amniocentesis, preterm premature rupture of membranes, randomized controlled trial, pregnancy

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Subclinical infection, characterized by colonization of amniotic fluid or membranes by pathogens without clinical evidence of overt infection, is found in one third of patients with PPROM.^{6,7} In utero exposure to infection or inflammation is associated with greater neonatal morbidity and higher rates of clinical chorioamnionitis and neonatal sepsis, important risk factors for cerebral palsy.^{8–11} Therefore, some authors have proposed performing amniocentesis prior to expectant management to rule out subclinical infection.^{12–14}

A systematic review of four studies comparing expectant management with intentional delivery in cases of PPROM was published in 2006.^{15–19} In those trials, where antibiotics and corticosteroids were not routinely used, intentional delivery was associated with a lower rate of chorioamnionitis and shorter maternal length of stay. Although expectant management was linked with greater gestational age at birth, the trials were unable to demonstrate any significant neonatal benefit.²⁰

One RCT compared expectant management with an approach using weekly amniocentesis in patients with PPROM.¹³ Delivery was planned when fetal lung maturity was detected or when MIAC was diagnosed by culture or gram stain. Management with weekly amniocentesis was associated with reduced neonatal length of stay. No RCT has compared the two management approaches (expectant management or intentional delivery) since use of antibiotics and corticosteroids became standard management in these patients.

The objective of the current study was to determine if women with PPROM between 28 and 34 weeks' gestation would agree to participate in a randomized trial comparing expectant management with management based on amniocentesis results. The second objective was to determine the role of several factors in their decision-making process.

METHODS

A qualitative prospective study was proposed to women who were admitted to our tertiary care centre between November 2005 and January 2007 at a gestational age of between 28 weeks 0 days and 34 weeks 6 days. Women were included if they were over 18 years of age, had a singleton pregnancy, and were able to read French. Women with a maternal or fetal condition that precluded expectant

Table 1. Patient demographic and obstetric characteristics

| | |
|--|------------|
| Age in years* | 28.5 ± 6.0 |
| Caucasian origin† | 34 (85) |
| Married or with partner† | 38 (95) |
| Education† | |
| Secondary | 21 (52.5) |
| College | 7 (17.5) |
| University | 12 (30) |
| Smoking† | 8 (20) |
| Gravidity‡ | 2 (1;8) |
| Parity‡ | 0 (0;4) |
| Gestational age at PPROM (in weeks)* | 30.4 ± 3.6 |
| Gestational age when answering the questionnaire (in weeks)* | 31.8 ± 2.0 |
| PPROM in a previous pregnancy† | 4 (10) |
| Mid-trimester amniocentesis in the current or a prior pregnancy† | 6 (15) |

*Mean ± standard deviation; †n (%); ‡Median (minimum; maximum).

management (suspected chorioamnionitis, suspected fetal distress, or lethal fetal anomalies) were not eligible. The project was approved by the Scientific and Ethics Committees of the Sainte-Justine Hospital Research Centre.

The first step of the study was the production of a booklet on PPROM for patients (containing information on PPROM, possible management strategies with their associated risks and benefits, differentiating between clinical and subclinical infections, amniocentesis technique, and the role and limits of markers in the detection of MIAC). A patient with PPROM, a resident in obstetrics and gynaecology, and a maternal-fetal medicine specialist reviewed the booklet to ensure that the information was clear to lay readers.

In the second step of the study, a questionnaire was developed using the same process. The first part of the questionnaire aimed to obtain demographic, medical, and obstetrical data, and the second part was designed to question the willingness of patients to participate in a hypothetical RCT that would compare expectant management with management based on amniocentesis results in patients with PPROM. In the latter situation, it was assumed that delivery would be indicated in cases when there was a high suspicion of MIAC based on direct (gram stain, cultures) or indirect (glucose, LDH, white blood cell count, or other potential available biomarkers) measures, or in which fetal pulmonary maturity was confirmed. Finally, women were asked to grade factors according to their importance in their decision-making process (0 = not important, to 5 = highly important).

ABBREVIATIONS

| | |
|-------|---|
| MIAC | microbial invasion of the amniotic cavity |
| RCT | randomized controlled trial |
| PPROM | preterm premature rupture of membranes |

Table 2. Comparison of patient demographic and obstetric characteristics according to their participation in a hypothetical RCT comparing expectant management to management based on amniocentesis results

| | Participation in the hypothetical RCT | | <i>P</i> |
|--|---------------------------------------|------------------|----------|
| | Yes (N = 28) | No (N = 12) | |
| Age in years* | 27.5 (24.0–32.5) | 28.5 (23.5–32.5) | 0.92 |
| Canadian origin† | 22 (78.2) | 12 (100) | 0.10 |
| Education† | | | |
| Secondary | 13 (46.4) | 8 (66.7) | 0.16 |
| College | 7 (25.0) | 0 | |
| University | 8 (28.6) | 4 (33.3) | |
| Smoking† | 4 (14.3) | 4 (33.3) | 0.21 |
| Gravidity* | 2 (1.3–3.0) | 2 (2–3.5) | 0.92 |
| Parity* | 0 (0–1) | 0 (0–1) | 0.65 |
| Gestational age at PPRM* | 32.2 (29.5–33.0) | 30.8 (29.2–32.2) | 0.46 |
| Gestational age when answering the questionnaire | 32.6 (30.5–33.6) | 31.2 (30.2–32.9) | 0.34 |
| PPROM in a previous pregnancy† | 3 (10.7) | 1 (8.3) | 0.99 |
| Previous amniocentesis† | 5 (17.5) | 1 (8.3) | 0.65 |

*Median (interquartile distribution); †n (%).

The booklet and the questionnaire were submitted to five eligible women who were asked to (1) answer the questionnaire, (2) evaluate each part on an anonymous evaluation grid developed by the authors, and (3) give any other comments about the clarity and/or the completeness of the booklet and questionnaire. No specific changes were suggested by these women. The study was presented to 35 other patients for a total of 40 women. The decision to recruit 40 patients was predetermined and based on the desire to complete this exploratory study in one year.

Patients were recruited by residents and maternal-fetal medicine specialists. The respondents remained anonymous, and the responses were analyzed only at the end of the study. Women who said they would agree to participate in the hypothetical trial were compared with those who said they would refuse. Statistical analyses were performed using SPSS 13.0 (SPSS Inc., Chicago, IL). Categorical variables were compared by means of the chi-square or Fisher exact test, and continuous variables were compared by means of the Mann-Whitney *U* test when appropriate. $P < 0.05$ was considered significant.

RESULTS

Forty women were recruited over a 15-month period. The demographic and obstetrical characteristics of the patients are shown in Table 1. Median gestational age at recruitment

was 31 weeks 6 days. All women read the information booklet and completed the written questionnaire.

The first question evaluated patients' preferences for the three options for their own care (expectant management vs. management with amniocentesis vs. participation in a study comparing the two previous strategies) if they were given the choice. Fifty-two percent (21/40) would have chosen amniocentesis, 33% (13/40) would have pursued expectant management without amniocentesis, and 15% (6/40) would have preferred to participate in a randomized study comparing the two possibilities. When the women were asked if they would participate in a RCT comparing the two management strategies (knowing that refusal to participate would lead to expectant management because it was the standard of care in our institution), 70% (28/40) said that they would agree to participate in such a hypothetical trial.

The demographic and obstetrical characteristics of women who would agree and those who would not agree to participate in a trial are shown in Table 2. No statistical differences were found between the two groups. Of the 28 women who would agree to a trial, 64% (18/28) would agree to a weekly amniocentesis, 29% (9/28) would not, and 7% (2/28) did not answer the question.

The median values recorded for reasons implied in their agreement to participate in the hypothetical trial are shown in Table 3. The main reasons were to determine if there was

Table 3. Classification of the reasons according to their importance in the decision-making process in patients who agreed to participate in the hypothetical RCT

| | Median | IQD |
|---|--------|---------|
| High importance (3 to 5) | | |
| I want to know if there is an infection | 5.0 | 5.0–5.0 |
| I want to know if my baby's lungs are mature | 5.0 | 5.0–5.0 |
| I want to participate in the advancement of knowledge in obstetrics | 4.0 | 3.0–5.0 |
| Having an amniocentesis gives me the feeling of doing more for my baby | 4.0 | 3.0–5.0 |
| Amniocentesis allows better management | 4.0 | 3.0–5.0 |
| I think that this study is the only way to know what is the best management in cases of PPRM | 4.0 | 3.0–5.0 |
| Having an amniocentesis allows me to better understand the cause of PPRM | 4.0 | 2.3–5.0 |
| Medium importance (2 to 3) | | |
| I would be worried about continuing my pregnancy without an amniocentesis | 3.0 | 1.0–4.0 |
| I would like to have an amniocentesis but the only way of perhaps having one is by participating in the study | 3.0 | 0.0–5.0 |
| Low importance (0 to 2) | | |
| I think that the medical team would be less interested in my case if I did not participate in the study | 0.0 | 0.0–1.0 |
| I think I will disappoint the medical team if I do not participate in the study | 0.0 | 0.0–0.8 |
| I do not feel free to refuse to participate in the study | 0.0 | 0.0–0.0 |

IQD: Interquartile distribution

an intra-amniotic infection or if fetal lung maturity was detected. The desire to improve their knowledge of obstetrical care was also important. Statements concerning the impression of receiving more active management with amniocentesis also received higher scores.

The median values recorded for reasons implied in subjects' refusal to participate in such a trial are shown in Table 4. The main reason for refusal was the fear that amniocentesis would be painful. The risks associated with amniocentesis (fetal trauma, cord puncture, iatrogenic labour) were also responsible for making patients reluctant to participate.

DISCUSSION

To our knowledge, this is the first study addressing the question of acceptability of management based on amniocentesis results in cases of PPRM. However, several previous studies have investigated the factors influencing patient participation in other clinical trials. Before giving consent, patients refer to their perceptions of the health care system, their past medical experiences, and their perceptions of their personal health status and of their treatment.^{20,21} The involvement of a pregnant woman brings special consideration because she needs to give consent

both for herself and for her fetus. She needs to weigh the risks and benefits for both of them.²²

Previous studies have examined the factors motivating pregnant women to participate in a clinical trial. The most important factor identified is potential benefit for the fetus, followed by potential benefit for the mother, and then altruism.^{23,24} The participation of pregnant women in a study for the advancement of science is conditional on the safety of the fetus. Factors related to possible improvement of the health of the fetus were most important, and the results obtained by our questionnaire concurred with previous reports in that respect.

Our study has a number of limitations. The first is that patients were asked about a hypothetical trial; their responses might have been different if they had been asked to actually participate. It is also possible that some important elements in their decision-making process were not included in the questionnaire. However, each patient was asked if she would have added a question or modified the questionnaire, but none had any element to add. Another potential limitation is that the questionnaire was distributed only in one centre. However, in the context of medical care in Canada, patients with PPRM at between 28 and

Table 4. Classification of the reasons according to their importance in the decision-making process in patients who refused to participate in the hypothetical RCT

| | Median | IQD |
|--|--------|---------|
| High importance (3 to 5) | | |
| I am afraid of the pain associated with amniocentesis | 5.0 | 3.3–5.0 |
| I am afraid that the needle will touch my baby or the cord during amniocentesis | 4.5 | 3.3–5.0 |
| I am afraid that amniocentesis will stimulate contractions | 4.5 | 3.0–5.0 |
| Medium importance (2 to 3) | | |
| I am afraid that amniocentesis will cause an infection | 3.0 | 2.3–4.0 |
| I am afraid that the markers will favour an infection when, in reality, there is no infection | 3.0 | 1.5–3.8 |
| I am afraid that the results of amniocentesis will not be conclusive | 3.0 | 1.3–3.0 |
| I am afraid that it is impossible to collect amniotic fluid | 3.0 | 1.0–5.0 |
| I am afraid that the markers will not suggest an infection when, in reality, there is an infection | 3.0 | 0.3–3.0 |
| I am afraid that the medical team will suggest induction because of an infection | 3.0 | 0.0–4.0 |
| I do not want to retrieve amniotic fluid because there is not much left | 2.5 | 1.0–4.0 |
| I want nature to decide the timing of my labour | 2.5 | 0.3–3.8 |
| I am against participating in a clinical trial when pregnant | 2.0 | 0.0–2.8 |
| Low importance (0 to 2) | | |
| I am afraid that I will not be able to withdraw from the trial if I want to | 0.5 | 0.0–2.5 |
| My partner does not want me to participate in the trial | 0.0 | 0.0–1.0 |

IQD: Interquartile distribution

34 weeks' gestation are usually managed in a tertiary centre with similar protocols.²⁵ It is also possible that some patients were not approached because of a very short latency period. Finally, data were not collected for women who refused to participate; however, we believe that they represent less than 20% of eligible patients.

CONCLUSION

In our institution, the majority of women between 28 and 34 weeks' gestation with PPROM would agree to participate in a RCT comparing expectant management with amniocentesis-based management. Our study allows us to conclude that such a study would be acceptable to our patient population and that the rate of participation would be over 50%.

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