Published in final edited form as:

Matern Child Health J. 2014 May ; 18(4): 858–863. doi:10.1007/s10995-013-1311-0.

Prevention of Recurrent Preterm Birth: Role of the Neonatal Follow-up Program

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Abstract

OBJECTIVES—Preterm birth (PTB) is a public health crisis in need of effective preventative strategies. Multi-disciplinary Neonatal Follow-up Programs (NFPs) provide health services to preterm infants at high risk for developmental problems after discharge from U.S. newborn intensive care units (NICUs). We aimed to determine whether NFPs are a potential effective venue for specialized maternal counseling and intervention aimed at reducing the high rate of recurrent PTB in this population.

METHODS—This prospective case series enrolled women with preterm children evaluated in the Utah Department of Health NFP, 2010-2012. Women were interviewed, received Maternal Fetal Medicine (MFM) counseling services, and maternal and neonatal records were abstracted. We assessed maternal demographics, medical history, and characteristics of the index pregnancy. We calculated the proportion of women with knowledge of PTB recurrence risk and available prevention strategies, and assessed current contraceptive use and reproductive plans.

RESULTS—Ninety-six women with a history of early PTB (< 26 weeks and/or birth weight <1250 gms) were evaluated. Nearly 1 in 5 women (19.8%) evaluated reported sexual activity, desire to avoid pregnancy, and no current contraceptive use, and were therefore at imminent risk of unintended pregnancy. Of women without permanent contraception, only 24.3% were aware of their individual PTB recurrence risk. Of women with a history of spontaneous PTB, only 4% were aware of effective pharmacologic preventative strategies.

CONCLUSIONS—Introduction of MFM consultation as part NFP multi-disciplinary services is a novel approach with the potential to reduce recurrent PTB in an exceptionally high-risk population.

Keywords

Department of Health; Maternal Fetal Medicine; Neonatal Follow-up Program; preterm birth; public health

INTRODUCTION

In 2009, 12.2% of infants in the United States were born preterm (<37 weeks gestation), and 3.5% were born at less than 34 weeks. While rates have dropped over the past 3 consecutive years, these improvements have been small, with only a 0.62% reduction in the rate of preterm birth (PTB) since 2006.¹ PTB remains the leading cause of infant mortality in the U.S.² Among survivors, the risk of serious long-term complications including cerebral palsy, neurodevelopmental delay, chronic lung disease, vision and hearing impairment is increased.² Given the persistent magnitude of this clinical challenge, novel PTB prevention strategies are desperately needed.

Premature birth may occur secondary to spontaneous labor (70-80%) or as a result of intervention for maternal or fetal problems (20-30%).³ Based on data from the Utah Population Database, women with a prior spontaneous PTB are at increased risk for recurrent PTB (at least 30%) and a history of early PTB (<34 weeks) is associated with the greatest risk of recurrence.⁴ Premature birth may also be secondary to fetal or maternal complications, such as preeclampsia. Recurrence risks for these complications vary widely, but exceed 50% in some instances.⁵

Successful strategies for prevention of recurrent spontaneous PTB may include standardized treatment in a PTB prevention clinic.⁶ This treatment includes administration of 17 alpha hydroxyprogesterone caproate (17P) from 16-36 weeks' gestation, which has been shown to decrease the rate of recurrent PTB by approximately one-third.^{7, 8} In cases of maternal or fetal complications which led to delivery, prenatal evaluation, close pregnancy surveillance, and appropriate intervention may decrease the risk of recurrent PTB. For example, treatment with low dose aspirin during pregnancy has been shown to reduce the risk of recurrent preeclampsia by approximately 10-15%.⁹

Across the U.S., multi-disciplinary neonatal follow-up programs (NFP) function to provide health services to infants at high risk for developmental problems after discharge from the newborn intensive care unit (NICU). Since premature delivery is the greatest perinatal risk factor for serious, long-term complications, the majority of infants evaluated in NFPs qualify secondary to extreme prematurity. Although multi-disciplinary pediatric services are provided, we are aware of no NFP in the nation that currently offers standardized high-risk obstetrical consultation (Maternal Fetal Medicine, MFM) or family planning services with the intent of reducing the rate of recurrent PTB.

With the above recurrence risks and potential for successful intervention in mind, MFM consult services began as a pilot program at the Utah Department of Health's Salt Lake City NFP in April 2010. Funding for the pilot program was provided by the Department of Obstetrics and Gynecology in the University of Utah School of Medicine. This program, nested within the Utah NFP, aims to:

1. Identify women with a high risk of recurrent PTB
2. Determine the most likely etiology of the PTB
3. Counsel parents regarding the estimated recurrence risk of PTB and potential fetal/maternal complications
4. Recommend appropriate inter-conception evaluation, prevention strategies and obstetrical management (including, but not limited to, uterine imaging to rule out uterine malformation, and counseling regarding smoking cessation, weight optimization, optimal inter-pregnancy interval, and progesterone during the next pregnancy)

5. Make appropriate referrals for further MFM care
6. Make appropriate referrals for family planning services

Our research objectives were to 1) characterize the obstetric risk factors for PTB in this high-risk population, 2) understand the obstetric and family planning needs of these women, and 3) gain insight into women's knowledge of PTB recurrence risk and available preventative strategies. Our over-arching goal was to ascertain whether the NFP clinic provides a useful 'window of opportunity' for maternal counseling and intervention aimed at reducing the high rate of recurrent PTB in this population.

MATERIALS AND METHODS

The Utah Neonatal Follow-Up Program (NFP) is sponsored by the Utah Department of Health (UDOH) and provides follow-up evaluation for infants and children who need special care after birth. The NFP addresses the medical, nutritional, neurologic, developmental and psychosocial needs of the preterm and high-risk infant after newborn intensive care unit (NICU) discharge. The mission of this statewide program is three-fold:

1. Offer 3 to 4 year interdisciplinary follow-up services to at-risk graduates from referring newborn intensive care units (NICUs),
2. Complement the care provided by the child's medical home, and
3. Provide feedback to the referring NICU.

Utah residents who are graduates of a NICU and who meet any the following criteria are eligible for enrollment: 1) birth weight $\geq$ 1250 grams, 2) gestational age of $\geq$ 26 weeks, 3) hypoxic ischemic encephalopathy¹⁰, 4) extracorporeal membrane oxygenation (ECMO). UDOH data suggest that approximately 50% of eligible preterm infants born in the State of Utah are seen in the Utah NFP (unpublished data). The Utah NFP offers periodic scheduled screening by a multi-disciplinary team including psychology, developmental pediatrics, nursing, nutrition, physical and occupational therapy, speech and language pathology, audiology, ophthalmology, social work, and neurology. The screening schedule includes visits at 3-4 months, 9 months, 18 months, 2 1/2 years, 3 1/2 years and 4 1/2 years (adjusted age for prematurity).

This prospective case series enrolled a convenience sample of women with children evaluated in the UDOH NFP Clinic. Women were eligible for inclusion in the study if they were seen for MFM consultation services during a regularly scheduled NFP screening visit. The MFM consultations were conducted one-half day per week between April 2010 and March 2012. Women were identified through screening daily NFP clinic schedules. No women were excluded from consultation. Institutional Review Board approval was obtained prior to enrollment.

Women were interviewed, received MFM counseling services and had abstraction of maternal and neonatal medical records. We used two strategies for performing the interview and counseling. A single MFM physician (EASC) with expertise in PTB prevention directly evaluated a subset of the cases. The remaining women were evaluated by a mid-level obstetrical care provider (TS; DNP, CNM with 8 years of MFM experience) in an attempt to improve cost-effectiveness of the intervention. The mid-level provider encounters were directly supervised by the MFM physician.

Although children born at term with a diagnosis of HIE, need for ECMO, or similar serious morbidity, are eligible for Utah NFP services, we limited data analysis to women with a history of PTB ($<$ 26 weeks and/or birth weight $<$ 1250 grams). Descriptive statistics were

used to assess maternal demographics, medical history, and index pregnancy characteristics. The proportion of women with *a priori* knowledge of PTB recurrence risk and available intervention strategies was calculated. Current contraceptive use and reproductive plans were assessed. Referrals were made, as indicated, for additional MFM and family planning services.

RESULTS

One-hundred and four women were included in the study, but 8 women were eligible for NFP services secondary to a child born at term with serious morbidity, as described above, and were excluded. Therefore, a total of 96 women with a history of PTB (≥ 26 weeks and/or birth weight <1250 grams), whose infants survived to NFP clinic participation, were included in the data analysis. The MFM physician directly evaluated 30 women. The remaining 74 patients were evaluated by the mid-level obstetric provider. A mean of 31.3 minutes was spent in consultation with each woman (SD 10.5; range 15-60 minutes).

Maternal demographic and index pregnancy characteristics are presented in Table 1. Approximately half of PTBs were due to spontaneous labor (56.3%, n=54), with the remainder secondary to maternal or fetal medical indication for iatrogenic preterm delivery.

Sixty-nine percent (n=66) of women identified a current relationship with a medical provider capable of providing women's health services. Only 64.6% (n=62) of women reported currently using contraception (Table 2). After excluding the 15.6% (n=15) of women who were pregnant at the time of assessment or who were attempting to become pregnant, 19.8% (n=19) reported sexual activity, desire to avoid pregnancy, and no current contraceptive use. This equates to nearly 1 in 5 women evaluated being at imminent risk for unintended pregnancy and subsequent recurrent PTB. In addition, although the number of women pregnant at the time of MFM evaluation was small (n=4), 50% (n=2) reported that the current pregnancy was not planned.

After excluding those currently pregnant or attempting pregnancy, 35.8% (n=29/81) of women were considering a pregnancy at some time in the future and were therefore particularly in need of MFM consultation services. Of women without permanent contraception, only 24.3% (n=19/78) had at least a general concept of their individual PTB recurrence risk (i.e. low, medium or high). Of women eligible for 17P for a history of spontaneous PTB (singleton or multiple gestation), only 4% (2/50) were aware that a medication was available that, if given during the next pregnancy, may reduce the risk of recurrent PTB.

After obstetrical consultation, 50% of women (n=48) were referred for additional MFM or family planning services (i.e. contraception). Decision for referral was prompted by 1) need for further medical evaluation prior to another pregnancy (e.g. uterine imaging to rule out uterine malformation as a contributing factor to PTB), 2) full MFM consultation (if the initial visit was with a mid-level provider and future pregnancy was desired), 3) a woman's desire for initiation of contraception or change to a more effective contraceptive, or 4) evaluation of a chronic medical condition (e.g. diabetes) that was likely to affect future pregnancy risks. Importantly, of those referred, only 16.7% (n=8/48) followed-up at the referral clinic within 3 months.

DISCUSSION

This prospective case series suggests that introduction of MFM consultation into NFP multi-disciplinary clinics has the potential to reduce recurrent PTB in an exceptionally high-risk

population. These data highlight an alarming risk of unintended high-risk pregnancy and low knowledge of recurrence risk and available preventative strategies among women with preterm children enrolled in the Utah NFP. Inclusion of MFM consultation into NFP clinics is a potentially high-impact public health initiative.

An analysis recently published in *The Lancet* recommended a conservative target of a relative reduction in preterm birth rates of 5% by 2015 in resource-rich countries.¹¹ Five interventions were cited as critical to this rate reduction: smoking cessation, decreasing multiple embryo transfers during ART, cervical cerclage, progesterone supplementation, and reduction of non-medically indicated labor induction or cesarean delivery. The President of the Association of State and Territorial Health Officials (ASTHO) Dr. David Lakey, has endorsed a goal of reducing prematurity by 8% by 2014 as part of the national Health Babies Project (www.astho.org/healthybabies/). ASTHO is collaborating with the Maternal Child Health Bureau of Health Resources and Service Administration (HRSA), the Association of Maternal and Child Health Programs, and the March of Dimes, among other programs, to develop a national strategy to reduce the preterm birth rate.

Achievement of these prematurity goals is contingent upon successful utilization of known effective strategies. Of the five recommended interventions cited in *The Lancet* article, the use of three (smoking cessation, cervical cerclage, and progesterone supplementation) could be facilitated by targeted preconception counseling, as proposed by this new initiative within the Utah NFP.

The primary risk factor for PTB is a history of PTB.^{4, 12, 13} However, as demonstrated in this prospective case series, many women are unaware of the presence and magnitude of this recurrence risk. It is imperative that these women be seen for MFM consultation before making decisions regarding future pregnancy. This is especially important for mothers with a history of a very early PTB, where the risk of recurrence is especially high.¹² Because the NFP focuses on early preterm neonates, this clinic is an optimal setting to ensure that maternal counseling regarding PTB etiology, individualized recurrence risk, and recommended preventive strategies occurs prior to the next pregnancy. Not all women seek regular health care services, and pediatric visits provide a unique window of opportunity to counsel women about PTB recurrence risk and preventative strategies. This study suggests that NFP clinics may be an effective venue for introduction of women's health services aimed at reducing the risk of recurrent PTB.

An ideal preterm birth prevention strategy would implement a multi-tiered approach with multiple points of counseling, including the maternal hospital stay, NICU stay, postpartum follow-up appointment, pediatric appointments (including NFP visits), and family home visits. Such an approach would ensure timely and appropriate counseling and should be the focus for future prospective interventions. While mid-level providers or primary care providers would be able to provide general health and family planning counseling to women at high-risk for recurrent PTB, MFM expertise is necessary to provide individualized risk assessment and prevention strategies given the potential complexity of decision-making in this population. Implementation of inter-conception care for high-risk women at NFP, or any venue, also should ideally include expertise to address psychosocial issues and provide general health assessments and intervention (such as nutrition evaluation and weight optimization). More comprehensive inter-conception care at NFP clinics may ultimately require a multi-disciplinary team of women's health experts working in parallel to the multi-disciplinary pediatric team. Such a comprehensive, multi-tiered approach was beyond the scope of this pilot program, but should be considered in future inter-conception care efforts.

This prospective case series was collected as a convenience sample, and was not a comprehensive evaluation of all women with children enrolled in the UDOH NFP. We attempted to evaluate all women during a given NFP clinic session. Nonetheless, the study design is a potential source of bias. While a randomized trial of maternal assessment and counseling would have been possible, we felt it was unethical to withhold counseling in this population of high-risk women. In addition, our objective was not to assess efficacy of the intervention, but rather to assess the obstetric and family planning needs of this population. Also, although all Utah neonates who meet NFP eligibility criteria at NICU discharge are referred to NFP, only a subset of infants ultimately enroll in this multi-disciplinary clinic. Therefore, our results should not be extrapolated to the larger population of early PTBs, but must be limited to the population who survive the immediate neonatal time period and who seek care at the Utah NFP. However, the programmatic goals of our initiative aim to help achieve the target reductions in preterm birth¹¹ and are generalizable to other NFP programs.

Our study has other weaknesses. Utah NFP records contained detailed information regarding the antenatal, delivery and NICU course from the referral hospital. Although we reviewed primary hospital records when possible to verify details of the PTB and diagnosis, we did not have access to hospital records for all subjects. We evaluated women at several time points (3 months to 4 1/2 years after the index delivery) and the relative distribution of these time points was not collected. This results in a relatively heterogeneous population and may influence the results we report.

Our study also had several strengths. Detailed data were prospectively collected during face-to-face interviews. To our knowledge, this is the first attempt to assess the potential value of MFM consultation as part of the multi-disciplinary services offered within the NFP setting. It proposes a novel approach to reduce recurrent PTB in an exceptionally high-risk population.

We have demonstrated that women with children enrolled in the Utah NFP secondary to extreme prematurity have an inadequate understanding of their PTB recurrence risk and available preventative strategies. In addition, almost 1 in 5 women evaluated were at imminent risk for unintended pregnancy and therefore also received contraceptive consultation and referrals. It is recommended that women with a prior obstetric complication have an inter-pregnancy interval of at least 18 months between delivery and subsequent conception in order to reduce the recurrence risk.^{14, 15} National data suggest that half of all pregnancies are unintended.¹⁶ An effective PTB prevention strategy therefore requires counseling regarding optimal inter-pregnancy interval and reduction of unintended pregnancy.

It is worth emphasizing that only a small fraction of women referred for additional services successfully followed through with those appointments. This highlights the potential value of comprehensive, on-site, women's health services at NFP clinics. Because of the intense demands of caring for children with special needs, NFP families may have additional barriers to obtaining women's health services. Offering consultation at the site of care for their children may increase access to MFM and family planning services and aid families in achieving healthy, optimally timed pregnancies.

The impact of MFM consultation services in the NFP setting is potentially significant through an approach including counseling regarding individualized recurrence risk, recommendations regarding preventative strategies in a subsequent pregnancy, optimization of the inter-pregnancy interval and prevention of unintended pregnancy. An ongoing MFM presence at NFP clinics may be an effective strategy to reduce the rate of PTB in the State of

Utah. Any reduction in recurrent PTB has the potential for significant improvements in long-term neonatal outcomes and substantial cost-savings.² A formal cost-effectiveness analysis is beyond the scope of the current study, but is planned prior to permanent integration of the program into the multi-disciplinary Utah NFP curriculum.

These preliminary data will be used to inform clinical care and future prospective research efforts aimed at reducing recurrent PTB. Further research is needed to determine whether systematic introduction of PTB prevention strategies into the NFP results in meaningful clinical improvements and overall cost-savings. Until then, these data provide evidence that introduction of MFM consultation, as a component of multi-disciplinary NFP clinics, may be a high-impact public service and an effective strategy for prevention of recurrent PTB.

At present, U.S. NFPs are multi-disciplinary clinics focused on the developmental needs of the high-risk neonate. Not currently addressed, is the ‘at-risk’ status of the family as a whole. Each family seen in NFP is at risk for recurrent obstetric/neonatal complications. A progressive approach would incorporate obstetric risk-reduction and preterm birth prevention strategies. These creative strategies would have the potential to significantly decrease the rate of recurrent PTB and associated infant morbidity and mortality. A reduction in recurrent PTB within NFP clinics may ultimately require a willingness to embrace the family, rather than the child, as the primary target for intervention and clinical care.

Acknowledgments

The authors thank Trece Swanson, DNP, CNM, for assistance with subject interviews and data collection (supported by the University of Utah Department of Obstetrics and Gynecology, Salt Lake City, Utah). They also thank the administration and staff of the Utah Department of Health Neonatal Follow-up Program in Salt Lake City, UT, for their support and facilitation of this project.

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Table 1
Maternal Demographic and Index Pregnancy Characteristics¹

Characteristic	
Maternal age, yrs, mean $\pm$ sd (range)	30.5 $\pm$ 6.3 (16-45)
Maternal race or ethnic group, n (%)	
White	73 (76)
Black	4 (4.2)
Hispanic	16 (16.7)
Other	3 (3.1)
Insured, n (%)	70 (75.3)
Private	64 (84)
Medicaid	11 (16.0)
Number of PTBs, n (%)	
1	74 (77.9)
2	19 (20)
3	2 (2.1)
Gestational age at index delivery, mean $\pm$ sd (range) ²	27.3 $\pm$ 2.5 (23-34)
Primary etiology of index PTB, n (%) ^{††}	
Spontaneous singleton	42 (43.8)
Multiple gestation	15 (15.6)
Preeclampsia	30 (31.2)
Fetal indication	9 (9.4)
Cesarean delivery n (%)	71 (74)
ART, n (%) ³	11 (11.5)

¹ Data analysis limited to women with PTBs (n=96). Data for all categories not available for all women; total numbers may therefore diverge from the total of 96.

² If women had more than one PTB and both infants were enrolled in the Neonatal Follow-up Program (NFP), the gestational age and etiology of the earliest PTB was analyzed.

³ Conception via assisted reproductive technology

Table 2
Family Planning Assessment^I

Characteristic	
Current contraceptive use, n (%)	62 (64.6)
Hormonal	11 (17.7)
Intrauterine device or implant	24 (38.7)
Barrier	9 (14.5)
Permanent sterilization of woman	16 (25.8)
Permanent sterilization of man	2 (3.2)
Pregnant, or attempting to get pregnant	15 (15.6)
Does not desire pregnancy, no current contraception	19 (19.8)

^I Data analysis limited to women with PTBs (n=96). Data for all categories not available for all women; total numbers may therefore diverge from the total of 96.