RISK FACTOR FOR UNSUCCESSFUL RATE OF PRETERM LABOR INHIBITION WITH TOCOLYTIC AGENT IN PREGNANT WOMEN 24⁰⁷-33⁶⁷ WEEKS OF GESTATION AT MAHARAT NAKHON RATCHASIMA HOSPITAL

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ABSTRACT

The objective is aimed to Assessing risk factors for unsuccessful rate of uterus contraction inhibition in pregnant women 24⁰⁷-33⁶⁷ weeks of gestation in Maharat Nakhon Ratchasima Hospital. The retrospective cohort study approved by the Research Ethics committee of, Maharat Hospital, Nakhon Ratchasima Province Thailand studying pregnant women who were diagnosed with preterm labor pain with gestational age of 24⁰⁷-33⁶⁷ weeks at the delivery ward of Maharat Nakhon Ratchasima Hospital and received Dexamethasone(corticosteroid) for the first time in every case between 1 January 2016 – 31 December 2018. From 361 pregnant women with preterm labor pain, 169 women were successful inhibition which was 54.29%. The group with failure inhibition were 165 women which was 45.71%. The factors relating to unsuccessful inhibition of uterus contraction were ANC less than 5 times, Adjusted odd ratios(AORs) 1.74; 95%CI 1.01-3.03, multiple pregnancy AORs 4.42 ; 95%CI 1.96-9.97 Cervical dilatation ≥ 3 cm AORs 5.93; 95%CI 3.44-10.22, the Effacement $\geq 80\%$, AORs 3.39; 95%CI 2.07-5.55, transfer from another hospital AORs 13.96; 95%CI 5.24-37.19. The research concludes that the factors relating to unsuccessful inhibition of uterus contraction were ANC less than 5 times, multiple pregnancy, Cervical dilatation ≥ 3 centimeters, Effacement $\geq 80\%$, and pregnant women referred from Secondary care center

KEYWORDS

Preterm Labor Pain, Successful Uterus Contraction Inhibition, Unsuccessful Uterus Contraction Inhibition,

INTRODUCTION

Preterm birth is a major obstetrics complication that can be a cause of newborn morbidity and mortality. Premature newborns are often found with several complications such as respiratory distress syndrome, intraventricular hemorrhage, early neonatal sepsis, poor physical development, and more risk of having cerebral disability. In addition to prolonged hospital stay and having to pay for a high cost of care, preterm cases are also found with consequences or complications on various systems that can affect the newborns long term, for instance problems on cognitive abilities, eyesight, general health, etc. [1].

According to National Institutes of Health(NIH)[2] the American College of Obstetricians and Gynecologists (ACOG), in 2016, the prevalence of preterm deliveries accounted for 12 percent of all births in the US [3]. In Thailand, according to data from the Bureau of Policy and Strategy, Ministry of Public Health, preterm deliveries were found at the rate of 10-12% [3]. At Maharat Nakhon Ratchasima Hospital, the incidences accounted for 9-10% of all births at the hospital.

In 2016, the ACOG recommended the use of single course of corticosteroid in pregnant women at 24⁰⁷-33⁶⁷ weeks of the gestation with premature labor to promote lung maturity, which would help provide them a greater chance of survival from premature birth. There were several types of tocolytic drugs in which the use was to be considered case-by-case based on gestational age, maternal and infant factors, and the medication side effects.

However, in some cases of premature labor, it was impossible to postpone the delivery for another 48 hours even when the preterm labor had been suppressed. Therefore, it was intriguing to study the relevant factors that may affect the failure of labor suppression in the treatment of premature labor, especially when this topic had never been studied before at Maharat Nakhon Ratchasima Hospital. The data obtained from this study can be further applied in the treatment of pregnant women with premature labor.

MATERIALS AND METHODS

The retrospective cohort study approved by the Research Ethics committee of, Maharat Hospital, Nakhon Ratchasima Province studying pregnant women who were diagnosed with preterm labor pain with gestational age of 24⁰⁷-33⁶⁷ weeks at the delivery ward of Maharat Nakhon Ratchasima Hospital and received Dexamethasone (corticosteroid) for the first time in every case between 1 January 2016 – 31 December 2018. The exclusion criteria were pregnant women who abortion as there was an indicator for delivered such as pregnancy harming the pregnant women, stillborn, severe fetal abnormalities, the women who received Dexamethasone for the second time and people

who had incomplete data in the hospital registry.

Maharat Nakhon Ratchasima Hospital is a tertiary care hospital which also accepts referrals from secondary care hospitals. In this research study, data were collected from the pregnant women's initial physical examination which would be categorized into "referral" and "non-referral" groups. Only the data of pregnant women with cervical dilation less than 3 cm at the initial examination would be collected. For the "referral" group, initial physical examination records at both the secondary care hospital and Nakhon Ratchasima Hospital would be collected.

The sample size was determined from a pilot study conducted on 15 pregnant women, and the principles of the "comparison of two independent proportions" were adopted. Based on the equation

$$N = z_1 - \frac{\alpha}{2} \sqrt{pq(1 + \frac{1}{r})} + z_1 - \beta \sqrt{p1q1 + \frac{p2q2}{r}} / \Delta^2$$

the minimum sample size for a single proportion was 108 or an equivalent of 216 for two independent proportions. Therefore, the data were collected through Maharat Nakhon Ratchasima Hospital consisting of the baseline characteristic data of the population, maternal age, number of pregnancy, antenatal care(ANC) data, single or multiple pregnancy, body mass index(BMI) during pregnancy, number of prescribed Dexamethasone before delivery, gestational age at delivered, membrane rupture, uterus contraction before birth, cervical dilatation and effacement, type and amount of tocolytic agent, receiving pain control or not, pregnancy complications, mode of delivered, neonatal weight at birth, Apgar score, neonatal complications, admission time in the hospital more than or less than 7 day, status of alive/dead before leaving the hospital.

Preterm labor is defined as uterine contraction at a frequency of 4 times in 20 minutes or 8 times in 1 hour which occurs together with cervical dilation of greater than 1 cm and cervical effacement equal to or greater than 80% at the gestational age of 24-33⁶⁷ weeks. Successful uterine contraction inhibition is defined as continuous inhibition of uterine contraction for 48 hours or longer or until 4 dosages of Dexamethasone have been administered. Unsuccessful uterine contraction inhibition is defined as inhibition of uterine contraction for less than 48 hours or if not all 4 dosages of Dexamethasone have been administered.

The statistical tests employed in this research consisted of Fisher's exact test for dichotomous variables and student's T-test for continuous variables. Moreover, Stata version 12 and SPSS Statistics version 25 was used for statistical data analysis. The result was considered statistically significant when p-value is lesser than 0.05.

Study result

It was found that pregnant women studying from 1 January 2016-31 December 2018 in the number of 361 people who were referred from adjacent hospitals in the amount of 107 people which was 29.6% and not referred from nearby hospitals in the number of 254 people which 70.4%. There were 196 cases of successful uterus contraction inhibition which was 54.29%. The group of unsuccessful uterus inhibition of 165 people which was 45.71%. It was found that the group referred from nearby hospital were unsuccessful for 57% and the number of not referring from nearby hospitals were 43% as shown in the table 1.

Table 1 baseline maternal characteristics of pregnant women

Variables	Inhibition success(n=196)	Inhibition failure (n=165)	p-value
Maternal age, mean $\pm$ SD.	26.95 $\pm$ 7.14	25.07 $\pm$ 7.12	0.013*
Nulliparous, n(%)	79 (40.3)	96 (58.2)	0.011*
Body mass index , mean $\pm$ SD.	24.54 $\pm$ 4.14	24.99 $\pm$ 4.65	0.332
Gestational age at admission, mean $\pm$ SD.	31.59 $\pm$ 2.06	31.26 $\pm$ 2.35	0.149
Prior preterm birth, n(%)	4 (2)	2 (1.2)	0.540
Number of Antenatal care <5 times, n(%)	43 (21.9)	55 (33.3)	0.015*
Number ANC2, mean $\pm$ SD.	6.89 $\pm$ 2.83	5.87 $\pm$ 3	0.001*
First ANC2 after 12 wk, n(%)	71 (36.2)	92 (55.8)	<0.001*
Anemia, n(%)	31 (15.8)	39 (23.6)	0.061
Multiple pregnancy	7 (4.2)	14 (7.1)	0.019*
Non-Refer	183 (93.4)	71 (43)	<0.001*
Refer	13(6.6)	94(57)	
Maternal urinary tract infection, n(%)	2 (1)	10 (6.1)	0.008*
Membrane rupture, n(%)	69 (35.2)	71 (43)	0.128
Cervical dilatation $\geq$ 3 cm	25 (12.8)	87 (52.7)	<0.001*
Effacement $\geq$ 80%, n(%)	51 (26)	103 (62.4)	<0.001*
Tocolytic (adalat), n(%)	188 (95.9)	156 (94.5)	0.540
Gestational age at delivery, mean $\pm$ SD.	32.24($\pm$ 7.58)	31.42($\pm$ 2.41)	0.153

*** Statistical significance t means used and Chi-square test used**

The basic information research participants as shown in the table 1, there were age of unsuccessful pregnant women less than the successful group with statistical significance, singleton pregnancy, number of ANC less than 5 times, first ANC after 12 weeks, multiple pregnancy, urinary tract infection, Cervical dilatation $\geq$ 3 cm, Effacement $\geq$ 80%, in the unsuccessful group more than the successful group with statistical significance.

Table 2 Neonatal outcomes

Variables	Inhibition success (n=196)	Inhibition failure (n=165)	p-value
APGAR score at the 1st minute < 7 mean $\pm$ SD.	7.92 $\pm$ 2.21	7.43 $\pm$ 2.01	0.026*
APGAR score at the 5th minute < 7 mean $\pm$ SD.	9.2 $\pm$ 2.12	9.06 $\pm$ 1.65	0.487
Birth weight < 2500 g, n(%)	159(81.1)	153(92.8)	0.010*
Neonatal complications			
Respiratory Distress Syndrome (RDS), n(%)	62 (29.2)	116 (68.6)	<0.001*
Early neonatal sepsis, n(%)	52(24.5)	83(49.1)	<0.001*
Neonatal jaundice, n(%)	62(29.2)	87(51.5)	<0.001*
Anemia, n(%)	4(1.9)	23(13.6)	<0.001*
Retinopathy of Prematurity (ROP), n(%)	8 (3.8)	9 (5.3)	0.466
Pneumonia, n(%)	6 (2.8)	11 (6.5)	0.084
Patent Ductus Arteriosus (PDA), n(%)	9 (4.2)	25 (14.8)	<0.001*
Hypoglycemia, n(%)	14 (6.6)	15 (8.9)	0.406
Necrotizing enterocolitis (NEC), n(%)	11(5.2)	17(10.1)	0.070

Neonatal urinary tract infection, n(%)	0 (0)	5 (3)	0.012*
Number of admission >7 days, n(%)	82(38.7)	120(71)	<0.001*
Early neonatal death, n(%)	5 (2.4)	16 (9.5)	0.003*

*** Statistical significance t means used and Chi-square test used**

The basic neonatal information research participants as shown in the table 2, it was found that birth weight < 2500 g, APGAR score at the 1st minute, respiratory distress syndrome, early neonatal sepsis, neonatal jaundice, anemia, patent ductus arteriosus, neonatal urinary tract infection, number of admission >7 days and early neonatal death in the unsuccessful group more than the successful group with statistical significance.

According to the results, there were statistically significant factor related to the unsuccessful uterus contraction inhibition the amount of ANC for less than 5 times, Adjusted odd ratios(AORs) 1.74; 95%CI 1.01-3.03, multiple pregnancy AORs 4.42; 95%CI 1.96-9.97, Cervical dilatation $\geq$ 3 cm AORs 5.93; 95%CI 3.44-10.22, Effacement $\geq$ 80% AORs 3.39; 95%CI 2.07-5.55, pregnant women referred from nearby hospitals AORs 13.96; 95%CI 5.24-37.19 as shown in the table 3.

Table 3 Risk factors of inhibition failure

Prognostic factors	Inhibition success N(%) /196	Inhibition failure N(%) /165	P-value	Adjusted OR (95% CI) #
Maternal age, mean $\pm$ SD.	26.95 $\pm$ 7.14	25.07 $\pm$ 7.12	0.421	1.01 (0.98-1.05)
Antenatal care <5 times	43(21.9)	55(33.3)	0.049*	1.74 (1.01-3.03)*
First antenatal care after 12 wks.	71 (36.2)	92 (55.8)	0.189	0.68 (0.38-1.21)
Multiple pregnancy	7 (4.2)	14 (7.1)	<0.001*	4.42 (1.96-9.97)*
Refer	183 (93.4)	71 (43)	<0.001*	13.96(5.24-37.19)*
Maternal urinary tract infection	2 (1)	10 (6.1)	0.563	2.32 (0.13-40.09)*
Cervical dilatation $\geq$ 3 cm.	25 (12.8)	87 (52.7)	<0.001*	5.93 (3.44-10.22)*
Cervical effacement $\geq$ 80%	51 (26)	103 (62.4)	<0.001*	3.39 (2.07-5.55)*

DISCUSSION

Prescribing of tocolytic to treat preterm labor pain with the pregnancy of 24⁰⁷-33⁰⁷ weeks was beneficial in extending the time for at least 48 hours to give the full course of Dexamethasone to promote fetal lung maturity in order to reduce respiratory distress syndrome and reduce neonatal morbidity and mortality of neonatal after delivery [2,3]. Therefore, to be able to extend the preterm labor pain for at least 48 hours could reduce complications to the neonatal after delivery. This study found that unsuccessful inhibition would have respiratory distress syndrome, early neonatal sepsis, neonatal jaundice, anemia, patent ductus arteriosus (PDA) with the admission for more than 7 days and higher death rate than successful group with statistical significance.

This study found the rate for successful preterm labor pain for at least 48 hours for 54.29% whereas the previous studies Theplib A. and Phupong V. found the rate for successful preterm labor pain at 83.4% [4] and the study of Kiasuda D. and colleague found the rate for successful preterm labor pain at 86.4% [5]. Maharat Nakhon Ratchasima Hospital is a tertiary referral hospital which accepts referrals from Secondary care center. The current coping method is that if there are pregnant women with preterm labor pain at a community hospital, they would receive Adalat as a loading dose and then sent to Maharat Nakhon Ratchasima Hospital. In this study, 361 pregnant women were found. 107 of them were referred from nearby hospitals which was 29.6% and 254 women were not referred from nearby hospitals which were 70.4%. It was found that referrals from nearby hospitals were one of the factors of this study which affected the unsuccessful inhibition AORs 13.96; 95%CI 5.24-37.19. Therefore, the future management in order to prevent this risk might require planning of nearby hospitals in preparing pregnant women before referrals and between referrals so that there would be a closer follow-up the condition of pregnant women.

From previous studies, it was found that much cervical dilatation, much cervical effacement could affect inhibit failure in the future [4][6]. This study found that the fact that the cervical dilatation ≥ 3 cm and cervical effacement $\geq 80\%$ affected the unsuccessful uterus contraction inhibition with statistical significance when adjusting AORs 5.93;95%CI 3.44-10.22, 3.39;95%CI 2.07-5.55 respectively. Recommending pregnant women to look out for uterus contraction for delivery and when it contracted they must come to the doctor as soon as possible, it might prohibit the contraction more successfully.

BMI of premature birth pregnant women were less than 18.5 found to be a factor in premature birth condition [7]. From this study, it was found that BMI of pregnant women in the whole group with successful inhibition and unsuccessful inhibition of uterus contraction had no difference with statistical significance and it was not related to unsuccessful inhibition of uterus contraction.

The frequency in ANC was a factor that was not related to preterm labor [8]. From this study, it was found that pregnant women with less than 5 ANC's for the entire pregnancy found in the group of unsuccessful uterus contraction inhibition more than the group of successful uterus contraction inhibition with statistical significance. It was found the relationship of unsuccessful uterus extraction AORs 1.74;95%CI 1.01- 3.03. The additional study on screening women and the quality of each ANC should give more information.

Multiple pregnancy would often find preterm labor [9]. In this study, it was found that the factor related to unsuccessful uterus contraction in this study were the condition of multiple pregnancy causing unsuccessful uterus contraction inhibition to increase with statistical significance AORs 4.42;95%CI 1.96-9.97. Therefore, finding of preterm labor in multiple pregnancy should be observed closely from antenatal care until finding preterm labor contraction in order to extend the time to prescribe corticosteroid at least 48 hours to reduce complications of the neonatal.

The history of preterm labor is another factor inducing preterm labor pain [10]. From this study, it was found that preterm labor history is not a factor relating to unsuccessful uterus contraction inhibition. It might be because it lacked details in recording medical registry and nowadays there is a treatment to prevent the next preterm labor.

The limit of this study is that as it is a retrospective cohort study so some data collection was not complete. Future data collection planning might enable collecting complete data. Moreover, collecting more data would enable us to find clearer data.

CONCLUSION

Prescribing uterus contraction inhibition to treat preterm labor contraction had factor related to unsuccessful uterus contraction inhibition with statistical significance which were ANC less than 5 times, multiple pregnancy, cervix opening ≥ 3 centimeters, cervical effacement $\geq 80\%$ and pregnant women referred from other hospital.

REFERENCE

1. F.Gary Cunningham et al.(2018). William Obstetrics, Preterm birth. (25th ed). United States of America: McGraw-Hill
2. Antenatal corticosteroids revisited: repeat courses. (2000). *NIH Consensus Statement*, 17(2), 1-18. Retrieved from <https://www.ncbi.nlm.nih.gov/pubmed/11725806> National Institutes of Health Consensus Development, P. (2001). Antenatal corticosteroids revisited: repeat courses - National Institutes of Health Consensus Development Conference Statement, August 17-18, 2000. *Obstet Gynecol*, 98(1), 144-150. doi:10.1016/s0029-7844(01)01410-7
3. American College of Obstetricians and Gynecologists' Committee on Practice Bulletins.(2016). Practice Bulletin No. 171: Management of Preterm Labor. Retrieved from <https://pubmed.ncbi.nlm.nih.gov/27661654/>
4. Theplib, A., & Phupong, V. (2016). Success rate of terbutaline in inhibiting preterm labor for 48 h. *J Matern Fetal Neonatal Med*, 29(5), 841-844. doi:10.3109/14767058.2015.1021671
5. Kiatsuda, D., Thinkhamrop, J., & Prasertcharoensuk, W. (2016). Success rate in preterm uterine contraction inhibition with tocolytic agents in a tertiary care center. *Int J Womens Health*, 8, 663-667. doi:10.2147/IJWH.S122781
6. Bastek, J. A., Sammel, M. D., Srinivas, S. K., McShea, M. A., Foreman, M. N., Elovitz, M. A., & Metlay, J. P. (2012). Clinical prediction rules for preterm birth in patients presenting with preterm labor. *Obstet Gynecol*, 119(6), 1119-1128. doi:10.1097/AOG.0b013e31825503e5
7. Girsan, A. I., Mayo, J. A., Carmichael, S. L., Phibbs, C. S., Shachar, B. Z., Stevenson, D. K., . . . March of Dimes Prematurity Research Center at Stanford University School of, M. (2016). Women's prepregnancy underweight as a risk factor for preterm birth: a retrospective study. *BJOG*, 123(12), 2001-2007. doi:10.1111/1471-0528.14027
8. Beeckman, K., Louckx, F., Downe, S., & Putman, K. (2013). The relationship between antenatal care and preterm birth: the importance of content of care. *Eur J Public Health*, 23(3), 366-371. doi:10.1093/eurpub/cks123
9. Kurdi, A. M., Mesleh, R. A., Al-Hakeem, M. M., Khashoggi, T. Y., & Khalifa, H. M. (2004). Multiple pregnancy and preterm labor. *Saudi Med J*, 25(5), 632-637. Retrieved from <https://www.ncbi.nlm.nih.gov/pubmed/15138532>

10. Dias TZ, Fava ML, PassiniJúnior R, Cecatti JG, Tedesco RP, Lajos GJ, Rehder PM, Nomura ML, Oliveira PF, Costa ML.Tocolysis among Women with Preterm Birth: Associated Factors and Outcomes from a Multicenter Study in Brazil:cross-sectional multicenter study. *Rev Bras Ginecol Obstet*. 2018 Apr; 40(4): 171-9.