Vaginal misoprostol before elective cesarean section for preventing neonatal respiratory distress: a randomized controlled trial

Ahmed M. Makhlouf, MD,[1] Abo Bakr A. Mitwaly, MD,[1] Ahmed Nasr, MD,[1] Esraa Badran, MD,[1] Samuel H. Ilya, MSc,[1] Ahmed M. Abbas, MD[1]

Keywords: Cesarean section, misoprostol, respiratory distress, prostaglandins

Abstract

Objective: The current study aims to evaluate the efficacy of vaginal misoprostol before elective cesarean section (ECS) for preventing the occurrence of neonatal respiratory distress (RD).

Materials and Methods: A randomized controlled trial (NCT03239327) was carried out in a tertiary-care university-affiliated hospital between June 2016 and August 2017. All eligible pregnant women scheduled for ECS were randomly allocated in a 1:1 ratio to two groups. One group, the Misoprostol group, received a misoprostol 50 mcg vaginal tablet 60 minutes before ECS while the other, the Control group, received no drugs before ECS. The primary outcome was the rate of neonatal RD among the study groups.

Results: The study included 146 women in each arm, with no significant difference between the baseline characteristics of members in each group. Primary outcomes resulted in 22 (15.1%) newborns in the misoprostol group having RD at birth versus 44 (30.1%) newborns with RD in the control (P =0.02). No differences were found between the groups regarding the need for neonatal intensive care unit (NICU) admission (P =0.61), duration of NICU stay (P =0.08) and neonatal mortality rate (P =0.73).

Conclusion: Prophylactic vaginal misoprostol at a dose of 50 mcg administered 60 minutes before ECS could reduce the rate of neonatal RD and improve the neonatal respiratory outcomes.

[1]Department of Obstetrics and Gynecology, Faculty of Medicine, Assiut University, Egypt

Introduction

Cesarean section (CS) is considered one of the most common surgical procedures worldwide as its rate has steadily increased over the last few years.[1] Additionally, neonatal respiratory distress (RD) resulting in death, which occurs in about 27% of cases,[4] is more prevalent among infants delivered by elective cesarean section (ECS) than after emergency CS or vaginal delivery.[2,3] The most frequent clinical presentations of neonatal RD are respiratory distress syndrome (RDS),

Please cite this paper as: Makhlouf AM, Mitwaly ABA, Nasr A, Badran E, Ilya SH, Abbas AM. Vaginal misoprostol before elective cesarean section for preventing neonatal respiratory distress: a randomized controlled trial. POG in Press. 2019 November; Article 1 [12 p.]. Available from: http://ir.uiowa.edu/pog_in_press/. Free full text article.

***Corresponding author:** Ahmed M. Abbas; MD, Department of Obstetrics and Gynecology, Woman's Health Hospital, Assiut University, Assiut, Egypt. Business telephone number: +20882414616, Fax: +20889202503. Cellular phone number: +201003385183. Postal code: 71511. E-mail: bmr90@hotmail.com*

***Financial Disclosure**: The authors report no conflict of interest.*

transient tachypnea of the newborn (TTN) and persistent pulmonary hypertension of the newborn (PPHN). RDS occurs in 1% of pregnancies due to qualitative or quantitative deficiency of surfactant production.[4] TTN is mainly attributed to delayed resorption of pulmonary fluid as a result of imperfect catecholamine surge.[5]

Catecholamines are known to promote surfactant secretion by acting on beta-adrenergic receptors in fetal lungs to increase their ability to reabsorb lung fluid.[6] However, infants born at term by ECS are deprived of the hormonal changes that protect them from RD.[7] This could be attributed to a defective catecholamine surge occurring at the onset of labor that increases surfactant production and lung fluid absorption.[8] This allows the neonatal respiratory system to be adapted for extra-uterine life. Prostaglandin administration before delivery can stimulate the catecholamine surge and thus reduce neonatal RD.[9] The most suitable time for its administration to provoke this effect before CS is still unknown. A previous study reported that vaginal administration of prostaglandin E2 gel 60 minutes before CS significantly increased the catecholamine levels in the fetal blood.[9]

A recent Cochrane review (2013) on the effect of prostaglandins before CS for preventing neonatal RD included only a single study on the application of vaginal prostaglandin E2 gel.[10] They expressed the need for further trials to determine the impact of prostaglandins on neonatal respiratory complications after ECS. A recent study by Khairy et al., 2017, reported that administration of 200 mcg of vaginal misoprostol at term, one hour before ECS, significantly reduced the occurrence of neonatal RD.[11]

Misoprostol is a prostaglandin E_1 analog that is available for cervical ripening before a variety of obstetric and gynecologic procedures.[12-15] One of its advantages is that it can be administered through multiple routes (oral, buccal, sublingual, vaginal, rectal).[16,17] However, an ideal dose and route for the administration of misoprostol remains unclear, with more than 30 different dosage regimens for its use among pregnant women described in the literature.[18]

Therefore, the current study aims to evaluate the efficacy of vaginal misoprostol before ECS for preventing the occurrence of neonatal RD.

Materials and Methods

Study type, settings and duration

The current study was a randomized, controlled trial (RCT) clinically registered at ClinicalTrials.Gov (NCT03239327). The study was conducted in Assiut University Women's Health Hospital, Egypt, between June 2016, and August 2017. The Assiut Medical School Ethical Review Board approved the study protocol. Written consent was obtained from all study participants before enrollment.

Study participants

We invited all pregnant women who attended the Antenatal Care Clinic of our hospital and were scheduled for ECS to participate in the study. Inclusion criteria limited study participants to

women aged 18 years or older, with an uncomplicated pregnancy at 34 to 37 weeks gestation, both with or without previous CS, carrying a singleton fetus with no major anomalies. Gestational age was confirmed with reliable early ultrasound measurement of crown-rump length. We excluded women with medical disorders, fetal distress or demise, and those scheduled for emergency CS. Additionally, women with any contraindication or sensitivity to prostaglandins and those who declined participation in the study were excluded.

Sample size

Sample size calculation was based on the incidence of neonatal severe RD requiring admission to a neonatal intensive care unit (NICU). Le Ray, et al., estimated the frequency of severe RD in ECS deliveries between 34 and 37 weeks to be 28%.[19] The 292 included study participants were divided into groups of 146 each. This sample size and the use of a two-sided chi-square test with α error of 0.05 suggested 80% power to detect a 50% reduction in the RD rate after vaginal administration of misoprostol (OR =0.50) (Epi-info™, CDC, USA. 2016).

Randomization

Women who met the inclusion criteria were randomly allocated, using sealed, coded, opaque and sequentially numbered envelopes containing computer generated random numbers into either the study group or the control group. One of the investigators retained the randomization envelopes and did not share in patients counseling or care. Allocation was never changed after patients were place in either the study or control group. The study was open-labeled so neither the investigators nor the participants were blinded.

Study intervention

At the time of recruitment, one of the study investigators collected basic data about participants including number of previous miscarriages, number of previous CS, indication of current ECS and gestational age at delivery. All women received two intramuscular doses of 12 mg dexamethasone (Epidron®;Eipico Pharma, Egypt) 12 hours apart, 48 hours before the scheduled time of ECS.

Eligible participants were randomly allocated in a 1:1 ratio to two groups. The study group consisted of women who received a misoprostol vaginal tablet 50 mcg (Misotac®; Sigma Pharma, SAE, Egypt) 60 minutes before ECS. The control group consisted of women who received no medications before ECS.

Follow-up

Continuous cardiotocographic monitoring was carried out after misoprostol administration to detect any evidence of uterine hyperstimulation and/or fetal distress. The surgical and anesthetic teams were in a state of complete readiness for the CS from the time of misoprostol administration. The anesthetic and surgical techniques were standardized for all women. Spinal anesthesia was used with preload of 500 ml saline and continuation of intravenous fluids throughout the operation. Regarding the surgical technique, all deliveries were performed through a transverse lower uterine

segment CS with delayed cord clamping (30 seconds after delivery). The same anesthetic and surgical team performed all the operations.

All deliveries were attended by a neonatology specialist, and details of the resuscitation at the operative theatre were recorded. Neonatal birth weight, heart rate, respiratory rate (RR), and Apgar scores at 1 and 5 minutes were recorded. Apgar score is usually used to represent the neonate's ability to initiate and maintain breathing after birth on a scale from zero to 10.[20] Apgar scores less than 3 indicate severe RD while scores between 4 and 6 indicate mild to moderate RD. There is no RD when the scores are between 7 and 10.

All neonates were assessed for signs of RD such as the presence of apnea, tachypnea, central cyanosis, chest wall retraction and nasal flaring[21] or signs of TTN (defined as a period of rapid breathing higher than the normal range of 40-60 times per minute).[22] All interventions performed by the pediatrician were recorded including, use of ambu-bag, endotracheal intubation, admission to the NICU and length of stay. Any case of neonatal mortality was recorded. The neonatal mortality rate was defined as the number of neonates that died from respiratory morbidity within one month of delivery.

Study outcomes

The primary outcome of this study was the rate of neonatal RD defined as RR>60 cycles per minute and/or signs of RD.[4] Secondary outcomes included Apgar scores at 1 and 5 minutes, the respiratory rate of the newborn, the incidence of apnea, the incidence of TTN, the need for mechanical ventilation of the neonate either by ambu-bag resuscitator or endotracheal intubation, the incidence of admission to NICU, the duration of NICU stay and the neonatal mortality rate.

Statistical analysis

Data entry and statistical analysis were done using SPSS software, Chicago, IL, USA, version 21. Categorical data were presented as frequency and percentage. Comparison between data in both groups was done by chi-square test. Continuous variables were compared using Student's *t*-test in the form of means ± standard deviation. Odds Ratio (OR) was estimated to evaluate clinical benefits from the administration of the drug used. Multivariate logistic regression analysis for the parameters affecting the rate of neonatal RD was carried out. P value < 0.05 was considered significant.

Results

We invited 304 women to participate in the study. Ten women were excluded as they did not meet the eligibility criteria. Moreover, two women declined participation in the study. We randomly assigned 292 women into the two study groups; 146 women in each arm (Figure 1: study flow chart).

Table 1 shows that both groups were homogenous regarding the baseline characteristics. The most common indication of ECS in both groups was repeat CS (77.4% of cases). No cases of uterine hyperstimulation or dehiscent CS scars were observed in either group.

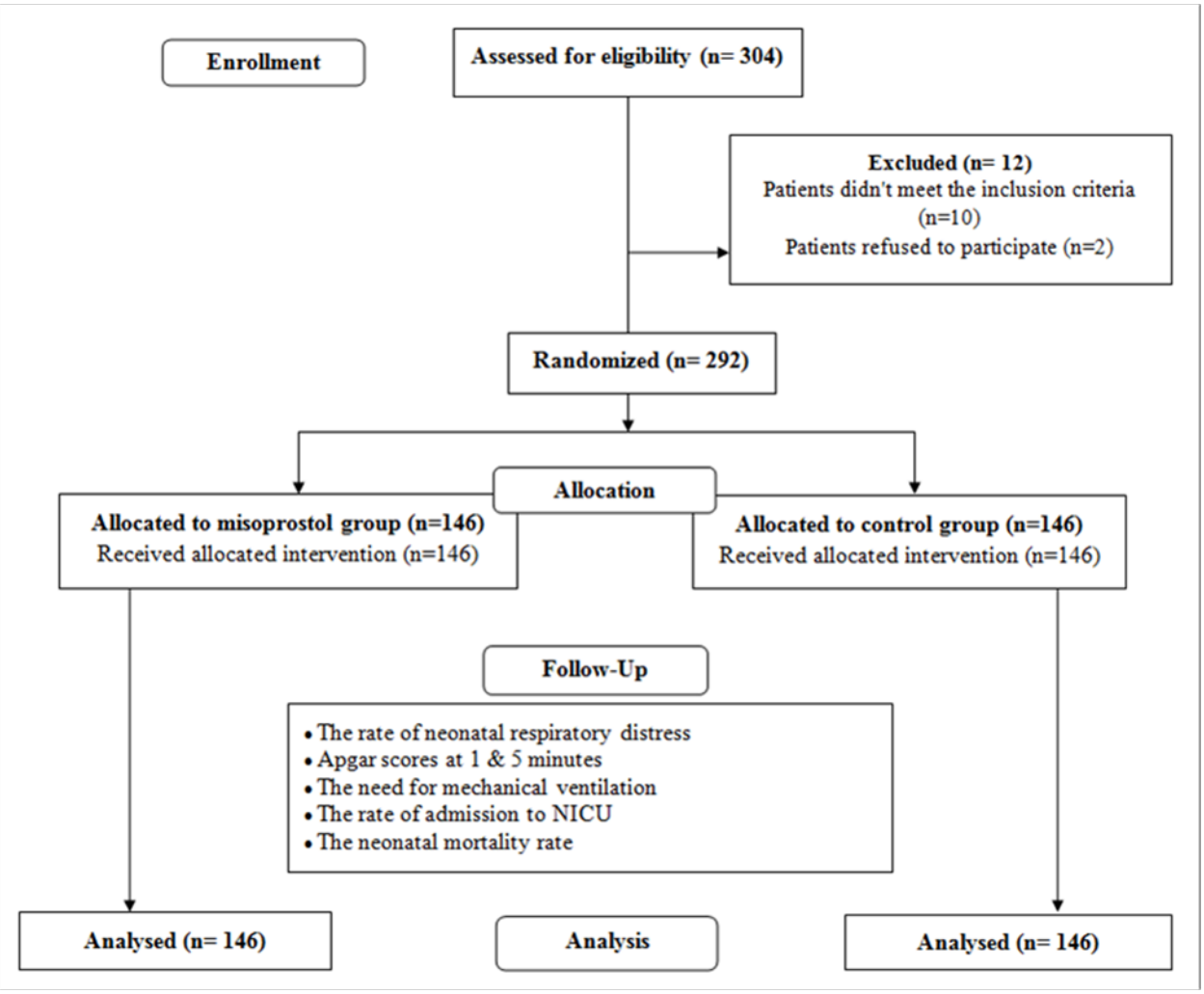

Figure 1: The study flowchart.

Table 1: The baseline characteristics of the study participants

Characteristics	Misoprostol group (n=146)	Control group (n=146)	P-value
Age **(years)**	27.52 ± 6.0	27.92 ± 5.95	0.64
Parity	2.36 ± 1.87	2.10 ± 1.92	0.33
Num. of previous miscarriages	1.01 ± 0.63	1.06 ± 0.75	0.47
Num. of previous CS	1.45 ± 1.28	1.38 ± 1.32	0.70
Gestational age at delivery **(weeks)**	35.81 ± 0.29	35.72 ± 0.39	0.19

CS; Cesarean section, All data are presented as mean ± standard deviation

Table 2 shows neonatal condition at birth. The respiratory rate in the misoprostol group was significantly lower than in the control group (43.2±8.3 vs. 54.1±10.6 cycles/min., respectively, p=0.01). There was no difference between the study and control groups regarding neonatal birth weight, heart rate, and Apgar scores at 1 & 5 minutes. Moreover, there was no difference regarding fetal gender in either group; 77 (52.7%) were male and 69 (47.3%) were female in the misoprostol group versus 71 (48.6%) males and 75 (51.4%) females in the control group (p= 0.92).

Table 2: The neonatal condition at birth in both study groups

Characteristics	Misoprostol group (n=146)	Control group (n=146)	P-value
Neonatal birth weight **(grams)**	2928 ± 356	2884 ± 412	0.47
Heart rate **(beats/min.)**	134.6 ± 11.3	131.2 ± 11.6	0.41
Respiratory rate **(cycle/min.)**	43.2 ± 8.3	54.1 ± 10.6	0.01*
Apgar score at 1 min.	8.7 ± 1.4	8.5 ± 1.5	0.46
Apgar score at 5 min.	9.4 ± 0.5	9.3 ± 0.6	0.31
Duration of NICU stay **(days)**	3.1 ± 1.2	3.3 ± 1.5	0.08

NICU; neonatal intensive care unit, All data are presented as mean ± standard deviation
* Statistical significant difference

Table 3: The neonatal outcomes in both study groups

Outcomes	**Misoprostol group (n=146)**	**Control group (n=146)**	**Odds ratio (95% confidence interval)**	**P-value**
Chest wall retraction	20 (13.7)	27 (18.5)	0.8 (0.62 - 1.09)	0.22
Nasal flaring	12 (8.2)	17 (11.6)	0.8 (0.6 -1.1)	0.34
Cyanosis	4 (2.7)	7 (4.8)	0.77 (0.49 - 1.23)	0.48
Apnea	1 (0.7)	6 (4.1)	0.57 (0.41 - 0.79)	0.04*
Respiratory distress **Severe (Apgar ≤ 3)** **Mild to moderate (Apgar 4-6)**	22 (15.1) 4 (2.7) 18 (12.3)	44 (30.1) 7 (4.8) 37 (25.3)	0.67 (0.54 - 0.85)	0.02*
TTN	22 (15.1)	38 (26)	0.7 (0.56 - 0.91)	0.01*
Need for ambu-bag	2 (1.4)	6 (4.1)	0.65 (0.43 - 0.99)	0.24
Need for intubation	0	4 (2.7)	0.49 (0.43- 0.55)	0.04*
Need for NICU admission	16 (11)	19 (13)	0.9 (0.65- 1.26)	0.61
Neonatal mortality rate	3 (2)	4 (2.7)	0.87 (0.45 - 1.67)	0.73

NICU; neonatal intensive care unit, TTN; transient tachypnea of newborn
All data are presented as number (%) *Statistical significant difference

Overall, the primary outcomes showed that 22 newborns (15.1%) in the misoprostol group had RD at birth versus 44 newborns (30.1%) in the control group, with a statistically significant difference between the two groups (p=0.02). The incidence of TTN and apnea were significantly higher in the control group than the misoprostol group (p=0.01 and 0.04 respectively). Other signs of RD such as chest wall retraction, nasal flaring and cyanosis showed no significant difference between each group (Table 3).

Only two newborns in the misoprostol group (1.4%) needed assisted ventilation by ambu-bag versus six newborns (4.1%) in the control group, with no statistical difference (p=0.24). On the other hand, four newborns (2.7%) in the control group needed endotracheal intubation versus none in the misoprostol group, with a statistically significant difference (p=0.04). Finally, there were no differences between the two groups regarding the need for NICU admission (p=0.61), duration of NICU stay (p=0.08) and neonatal mortality rate (p=0.73) (Table 3).

Multivariate logistic regression analysis done for the predictors of neonatal RD revealed that maternal age, parity and indication of CS were not predictors for occurrence of neonatal RD. In fact, gestational age at delivery and use of misoprostol before CS were the only parameters that independently affected the rate of neonatal RD (p=0.001 and 0.026, respectively) (Table 4).

Table 4. Multivariate logistic regression analysis for the predictors of neonatal respiratory distress

Predictors	Unstandardized Coefficients		Standardized Coefficients Beta	Odds ratio	P value
	B	Std. Error			
(Constant)	41.020	8.475			0.000
Age	0.022	0.030	0.053	1.022	0.466
Parity	0.744	0.464	0.56	0.475	0.109
Indication of CS	0.631	0.744	0.718	0.958	0.532
Gestational age	-1.169	0.237	0.523	0.311	0.001*
Use of misoprostol	-0.805	0.362	-0.339	0.447	0.026*

*** Statistical significance at P <0.05**

Discussion

In this randomized controlled study, we demonstrated that administration of 50 mcg vaginal misoprostol 60 minutes before ECS at 34 to 37 weeks gestation may decrease the rate and severity of neonatal RD. To the best of our knowledge, this is the first study evaluating the effect of misoprostol administration on neonatal respiratory outcomes before ECS at 34 to 37 weeks gestation.

RD is the main cause of early neonatal morbidity and mortality and frequently accounts for the high cost of neonatal intensive care.[23] Thus, term newborn delivery by ECS rather than vaginally leads to a two- to four-fold increase in risk for neonatal respiratory morbidity.[24]

Earlier animal studies demonstrated the beneficial effect of prostaglandins on the respiratory function. Torday et al., reported that prostaglandin E2 integrated the effects of fluid distension and glucocorticoids on lung maturation.[25] Additionally, Zaremba et al., reported that administration of prostaglandin F2 alpha analogue to pregnant cows before labor accelerated fetal lung maturation and improved respiratory function after birth.[26]

With the current rapid rise of CS worldwide, we recognize the urgent need for studying the neonatal respiratory complications. While ECS is a well-known risk factor for different forms of neonatal RD, other confounding factors may add to the development of neonatal RD after CS. These may include neonatal gender, birth weight, type of anesthesia, administration of steroids and maternal medical disorders.[27] In the current study, women with medical disorders were excluded. Additionally, all participants received a prophylactic dose of corticosteroids and delivered under spinal anesthesia. Furthermore, there were no significant differences between the study and control groups regarding neonatal gender or birth weight.

The Cochrane review published in 2013 included only one study about the use of prostaglandins before CS for preventing neonatal RD.[10] In 2004, a RCT involving 36 women, by Singh and colleagues in Australia, showed that prophylactic administration of 2 mg vaginal prostaglandin E2 gel 60 minutes before ECS at ≥ 38 weeks gestation significantly increased noradrenaline concentrations in umbilical arterial blood with no difference in adrenaline concentration nor the arterial and venous pH.[9] In this study, only one neonate in the control group developed TTN versus none in the prostaglandin E2 group. However, this study has no significant impact as it could not assess any of the clinical neonatal outcomes due to its small sample size. The results of the current study might, therefore, be included in the next Cochrane reanalysis.

In 2017, Khairy et al., in Egypt conducted a large RCT that included 120 women to determine whether administration of prostaglandin E1 (misoprostol) 200 mcg before ECS would decrease neonatal respiratory complications.[11] The rate of TTN was significantly lower in the misoprostol group as compared with the control group (0% versus 21.7%, respectively;

p=0.000). Our study agreed with their results as the rate of TTN was 15.1% versus 26% in the misoprostol and control groups respectively (p=0.01). However, they also found a significant decrease in the rate of admission to NICU and duration of NICU stay with misoprostol administration (p<0.001). Additionally, the Apgar scores at 1 and 5 minutes were significantly lower in the misoprostol group (p=0.016 and 0.001 respectively). Finally, no cases of RD occurred in the misoprostol group in their study.[11]

These results contrast with those of our study. However, it should be noted that the dose of misoprostol used was different and the gestational age (≥at 38 weeks) at ECS was later than in our study. Also, the larger sample size in the current study may have led to the difference in our results. We believe that using such a high dose of misoprostol (200 mcg) could be associated with serious maternal complications that outweigh its benefit. In the current study, the choice of using 50 mcg misoprostol was not associated with uterine hyperstimulation or scar dehiscence.

The strengths of our study include that it was a RCT that included a large sample of women. Also, we were able to recruit our calculated sample so that we could achieve sufficient power to detect a clinically significant difference in our primary outcome. Finally, the use of misoprostol, which is inexpensive and has no major side effects compared with its proven benefits in neonatal respiratory outcomes, is another merit.

The main limitation of our study was probably related to the lack of blinding of the surgeon and participants during randomization. However, the neonatologist who assessed the neonatal respiratory outcomes was blinded by the study group. Also, we did not compare neonatal outcome at different gestational ages in order to show the most beneficial time for misoprostol administration since the sample size did not allow subgroup analysis. Additionally, we did not measure the blood pH or catecholamine concentration in the umbilical cord arterial blood after delivery. Further studies are needed to confirm our results and to compare the effect of misoprostol on different gestational ages after 37 weeks.

In conclusion, prophylactic vaginal misoprostol 50 mcg before elective CS at 34-37 weeks gestation reduces the rate of neonatal respiratory morbidity and could be an efficient way to prevent neonatal RD.

References

1. Tampakoudis P, Assimakopoulos E, Grimbizis G, Zafrakas M, Tampakoudis G, Mantalenakis S, Bontis J. Cesarean section rates and indications in Greece: data from a 24-year period in a teaching hospital. Clin Exp Obstet Gynecol. 2004;31(4):289-92. PubMed PMID: 15672970.

2. Zanardo V, Simbi AK, Franzoi M, Soldà G, Salvadori A, Trevisanuto D. Neonatal respiratory morbidity risk and mode of delivery at term: influence of timing of elective caesarean delivery. Acta Paediatr. 2004 May;93(5):643-7. https://doi.org/10.1111/j.1651-2227.2004.tb02990.x PubMed PMID: 15174788.

3. Hansen AK, Wisborg K, Uldbjerg N, Henriksen TB. Risk of respiratory morbidity in term infants delivered by elective caesarean section: cohort study. BMJ. 2008 Jan 12;336(7635):85-7. Epub 2007 Dec 11. https://doi.org/10.1136/bmj.39405.539282.BE PubMed PMID: 18077440; PubMed Central PMCID: PMC2190264.

4. Respiratory Distress Syndrome (RDS). In: Intensive Care Nursery House Staff Manual. UCSF Children's Hospital at UCSF Medical Center. The Regents of the University of California; 2004. P. 79-84. https://www.ucsfbenioffchildrens.org/pdf/manuals/25_RDS.pdf

5. Bland RD, Carlton DP, Jain L. Lung fluid balance during development and in neonatal lung disease. In: Bancalari E, Polin RA editors. The Newborn Lung: Neonatalogy Questions and Controversies. 1st Edition. Philadelphia: Saunders; 2008: p. 141–165.

6. Faxelius G, Hägnevik K, Lagercrantz H, Lundell B, Irestedt L. Catecholamine surge and lung function after delivery. Arch Dis Child. 1983 Apr;58(4):262-6. https://doi.org/10.1136/adc.58.4.262 PubMed PMID: 6847229; PubMed Central PMCID: PMC1627967.

7. Jain L, Eaton DC. Physiology of fetal lung fluid clearance and the effect of labor. SeminPerinatol. 2006 Feb;30(1):34-43. https://doi.org/10.1053/j.semperi.2006.01.006 PubMed PMID: 16549212.

8. Abdelazim I, Farghali MMM, Elbiaa AAM, Abdelrazak KM, Hussain M, Yehia AH, Rashad M. Impact of antenatal oxytocin infusion on neonatal respiratory morbidity associated with elective cesarean section. Arch Med Sci. 2017 Apr 1;13(3):629-634. https://doi.org/10.5114/aoms.2017.67292Epub 2017 Apr 20. PubMed PMID: 28507580; PubMed Central PMCID: PMC5420644.

9. Singh M, Patole S, Rane A, Naidoo D, Buettner P. Maternal intravaginal prostaglandin E2 gel before elective caesarean section at term to induce catecholamine surge in cord blood: randomised, placebo controlled study. Arch Dis Child Fetal Neonatal Ed. 2004 Mar;89(2):F131-5. https://doi.org/10.1136/adc.2002.025957 PubMed PMID: 14977896; PubMed Central PMCID: PMC1756045.

10. Motaze NV, Mbuagbaw L, Young T. Prostaglandins before caesarean section for preventing neonatal respiratory distress. Cochrane Database Syst Rev. 2013 Nov 11;(11):CD010087. https://doi.org/10.1002/14651858.CD010087.pub2 PubMed PMID: 24218013.

11. Khairy HT, El-Mekkawi SF, El-Kotb AM, El-Sorady SI. Misoprostol before elective caesarean section for decreasing the neonatal respiratory morbidity: a randomized control trial. Egypt J Hosp Med. 2017; 68: 878-884. https://doi.org/10.12816/0038186

12. Othman ER, Fayez MF, El Aal DE, El-Dine Mohamed HS, Abbas AM, Ali MK. Sublingual misoprostol versus intravenous oxytocin in reducing bleeding during and after cesarean delivery: A randomized clinical trial. Taiwan J Obstet Gynecol. 2016 Dec;55(6):791-795. https://doi.org/10.1016/j.tjog.2016.02.019 PubMed PMID: 28040121.

13. Abbas Mitwaly AB, Abbas AM, Abdellah MS. Intra uterine extra-amniotic versus vaginal misoprostol for termination of second trimester miscarriage: A randomized controlled trial. Int J Reprod Biomed (Yazd). 2016 Oct;14(10):643-648. https://doi.org/10.29252/ijrm.14.10.643 PubMed PMID: 27921088; PubMed Central PMCID: PMC5124327.

14. Abdellah MS, Abbas AM, Hegazy AM, El-Nashar IM. Vaginal misoprostol prior to intrauterine device insertion in women delivered only by elective cesarean section: a randomized double-blind clinical trial. Contraception. 2017 Jun;95(6):538-543. https://doi.org/10.1016/j.contraception.2017.01.003Epub 2017 Jan 11. PubMed PMID: 28088498.

15. Samy A, Abbas AM, Mahmoud M, Taher A, Awad MH, Hussein M, Ramadan M, Shalaby MA, Hatem D, Wali AA, Hussein AH. Evaluating different pain lowering medications during intrauterine device insertion: a systematic review and network meta-analysis. Fertil Steril. 2019 Mar 1;111(3):553-61. https://doi:10.1016/j.fertnstert.2018.11.012. Epub 2019 Jan 2. PubMed PMID: 30611553.

16. Borgatta L, Kapp N; Society of Family Planning. Clinical guidelines. Labor induction abortion in the second trimester. Contraception. 2011 Jul;84(1):4-18. https://doi.org/10.1016/j.contraception.2011.02.005Epub 2011 Mar 30. PubMed PMID: 21664506.

17. Shady NW, Sallam HF, Elsayed AH, Abdelkader AM, Ali SS, Alanwar A, Abbas AM. The effect of prophylactic oral tranexamic acid plus buccal misoprostol on blood loss after vaginal delivery: a randomized controlled trial. J Maternal-Fetal Neonat Med. 2019;32(11):1806-12. https;//doi:10.1080/14767058.2017.1418316. Epub 2017 Dec 27. PubMed PMID: 29241383.

18. Wildschut H, Both MI, Medema S, Thomee E, Wildhagen MF, Kapp N. Medical methods for mid-trimester termination of pregnancy. Cochrane Database Syst Rev. 2011 Jan 19;(1):CD005216. https://doi.org/10.1002/14651858.CD005216.pub2 PubMed PMID: 21249669.

19. Le Ray C, Boithias C, Castaigne-Meary V, l'Hélias LF, Vial M, Frydman R. Caesarean before labour between 34 and 37 weeks: what are the risk factors of severe neonatal respiratory distress? Eur J ObstetGynecolReprod Biol. 2006Jul;127(1):56-60. https://doi.org/10.1016/j.ejogrb.2005.09.005Epub 2005 Oct 21. PubMed PMID: 16243426.

20. Harrison VC. The Newborn Baby. 5th ed. Cape Town: Juta& Company Ltd; 2008.

21. Edwards MO, Kotecha SJ, Kotecha S. Respiratory distress of the term newborn infant. Paediatr Respir Rev. 2013 Mar;14(1):29-36; quiz 36-7. https://doi.org/10.1016/j.prrv.2012.02.002 Epub 2012 Mar 2. PubMed PMID: 23347658.

22. Warren JB, Anderson JM. Newborn respiratory disorders. Pediatr Rev. 2010 Dec;31(12):487-95; quiz 496. https://doi.org/10.1542/pir.31-12-487 PubMed PMID: 21123510.

23. Miracle X, Di Renzo GC, Stark A, Fanaroff A, Carbonell-Estrany X, Saling E; Coordinators Of World Associatin of Perinatal Medicine Prematurity Working Group. Guideline for the use of antenatal corticosteroids for fetal maturation. J Perinat Med. 2008;36(3):191-6. https://doi.org/10.1515/JPM.2008.032 PubMed PMID: 18576926.

24. Hansen AK, Wisborg K, Uldbjerg N, Henriksen TB. Elective caesarean section and respiratory morbidity in the term and near-term neonate. Acta ObstetGynecol Scand. 2007;86(4):389-94. https://doi.org/10.1080/00016340601159256 PubMed PMID: 17486457.

25. Torday JS, Sun H, Qin J. Prostaglandin E2 integrates the effects of fluid distension and glucocorticoid on lung maturation. Am J Physiol. 1998 Jan;274(1):L106-11. https://doi.org/10.1152/ajplung.1998.274.1.L106 PubMed PMID: 9458807.

26. Zaremba W, Grunert E, Aurich JE. Prophylaxis of respiratory distress syndrome in premature calves by administration of dexamethasone or a prostaglandin F2 alpha analogue to their dams before parturition. Am J Vet Res. 1997 Apr;58(4):404-7. PubMed PMID: 9099388.

27. van den Berg A, van Elburg RM, van Geijn HP, Fetter WP. Neonatal respiratory morbidity following elective caesarean section in term infants. A 5-year retrospective study and a review of the literature. Eur J ObstetGynecolReprod Biol. 2001 Sep;98(1):9-13. https://doi.org/10.1016/S0301-2115(01)00292-5 PubMed PMID: 11516792.