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Misoprostol before Elective Caesarean Section for Decreasing the Neonatal Respiratory Morbidity: A Randomized Control Trial

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ABSTRACT

Background: neonatal respiratory morbidities are common neonatal outcome the worrisome the mothers the most when approaching labour. They vary in clinical presentations with various long term effects, the most importantly related to caesarean section are Transient Tachypnea of the Newborn (TTN), Respiratory Distress Syndrome (RDS), Persistent Pulmonary Hypertension (PPHN). **Aim of the Work:** the aim of this study is to assess the efficacy of Misoprostol or the Prostaglandin E1(PGE1) on the reduction of the neonatal respiratory morbidity in women scheduled for term caesarean section (38-38^{+6} weeks Gestational Age (GA).

Patients and Methods: this is a Randomized Controlled Trial (RCT) which was conducted over six months from November 2016, to April 2017 on 120 pregnant women who were approached before elective caesarean section (ECS), managed in Ain Shams University Maternity Hospital (ASUMH), and their neonates followed up in the Neonatal Intensive Care Unit (NICU) of Ain Shams University Maternity Hospital to assess the effect of Misoprostol when given for women one hour before their scheduled caesarean section upon reducing the neonatal respiratory morbidity.

Results: the current study revealed a highly statistically significant difference between groups according to respiratory morbidity, and especially the TTN using Chi-square test, with p-value <0.001 Highly Significant.

Conclusion: the study concluded that when a vaginal tab containing Misoprostol 200 microgram given to women one hour before term elective caesarean section between 38-38^{+6} weeks compared to placebo, it simulates the normal labour to enable the neonate through catecholamines surge, and thus surfactant secretion for better adaptation to the extrauterine life.

Recommendations: Misoprostol can be administered vaginally to candidate pregnant women with term pregnancies with certain inclusion criteria before an elective caesarean section (after exclusion of any contraindication and thorough good history taking and clinical examination) in order to reduce the neonatal respiratory morbidity and especially the transient tachypnea of newborn. Thus, decrease the duration of neonatal NICU admission and mortality.

Keywords: neonatal respiratory morbidities, TTN, RDS, PPHN, PG, Misoprostol, cesarean section, GA, NICU.

INTRODUCTION

Neonatal respiratory morbidities may occur in either term or preterm newborns with a higher relative risk in preterm, and whether born vaginally or through caesarean section, but in a higher percentage after elective caesarean section whose rate is rising either due to maternal request**,** obesity**,** and older maternal age than after normal vaginal delivery [(1)] or emergency caesarean section [(2)]. It is responsible for 30% of neonatal deaths [(3)]**.**

It has several subdivisions: one is the respiratory distress syndrome (RDS) which is called hyaline membrane disease, it can occur in about 1% of pregnancies as a result of a pathology in lung surfactant either qualitative or quantitative [(3)]**,** and usually in preterm neonates [(4)]**.** Another is transient tachypnea of the newborn (TTN) in which there is respiratory distress and increased respiratory rate due to delayed resorption of pulmonary fluid, as a result of defective catecholamine surge [(5)]**,** its incidence is 5.7/1000 deliveries (95% CI;1.7-2.7) in a review of 33,289 term deliveries (37 to 42 weeks) in London, UK, with a higher incidence in the elective caesarean section group (35.5/1000) compared to
(12.2/1000) after C.S during labour and (5.3/1000) born vaginally [(6)]**.** And also includes persistent pulmonary hypertension (PPHN) in which the fetal pulmonary vascular resistance remains high and the pulmonary blood flow still low after delivery [(3)]**.**

Physiologically, Catecholamines can stimulate pulmonary fluid absorption through acting upon beta-adrenergic receptors in fetal lung which present more late in gestation [(5)]**,** and thus enable the secretion of surfactant [(3)]**.** This surge of catecholamines can be provoked through prostaglandins given before caesarean

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section to pregnant females [8] as those who are born vaginally are found to be adapted metabolically through a higher catecholamine level at birth [8]. So, prostaglandins may be given about one hour before an elective caesarean section after excluding the presence of any contraindication to their use to decrease the neonatal respiratory diseases and thus, the number of children who suffered from bronchopulmonary dysplasia that occurs frequently in children who had previously TTN will diminish [3].

The prostaglandins in common use are Misoprostol (prostaglandin E1) and Dinoprostone (prostaglandin E2) [11] .Prostaglandin E1 (Misoprostol) is available as a cervical ripening agent in the form of 100 or 200 mcg tablets which can be taken orally, vaginally, or sublingually, their Tmax is 12 ± 3 minutes with terminal half life ranging from 20 to 40 minutes [9]. Prostaglandins E2 which are available as oral tablets, pessaries, or vaginal gels are uteroselective agents widely used for induction of labour, start action within 10 minutes and become in full action after about 12 hours [10].

In a previous prospective study of 36 women scheduled for an elective caesarean section beyond 38weeks [11], 18 women received intravaginal prostaglandin E2 gel and 18 received placebo, there was one neonatal respiratory distress case in the control group which was reported as transient tachypnea of the newborn (risk ratio (RR) 0.33, 95% confidence interval (CI) 0.01 to 7.68) with similar Apgar score at one and five minutes and no need to mechanical ventilation nor side effects related to treatment in either group, so no difference in respiratory outcome reported although there was a significantly higher catecholamine level in the intervention group.

AIM OF THE WORK

The aim of this study is to assess the efficacy of Prostaglandin E1 on the reduction of the neonatal respiratory morbidity in women scheduled for term caesarean section (38-38^{+6} weeks gestational age).

PATIENTS AND METHODS

This is a Randomized Controlled Trial (RCT) which was conducted over six months from November 2016 to April 2017 on pregnant women who were approached before elective caesarean section, managed in ASUMH, and their neonates followed up in the NICU of ASUMH to assess the effect of Misoprostol when given for women one hour before their scheduled caesarean section upon reducing the neonatal respiratory morbidity.

Study Population

The study population comprises one hundred and twenty (120) pregnant women scheduled for caesarean section, fulfilling the inclusion criteria, in ASUMH, during the study period.

Sample Size Justification

The required sample size has been estimated using the Statistical Package for the Social Science the International Business Machines Corporation (IBM SPSS Sample Power, V. 3, July, 2010, IBM SPSS statistics, IBM Corp., USA.).

After reviewing previous trial [11] results on a very small size which was very poor regarding the statistical results, no definite conclusion could be obtained from, and as no previous studies on assessing the neonatal respiratory morbidity after misoprostol giving, sample size would be calculated according to the power of test during sampling. So, the power of the test will be reevaluated every 50 pregnant women that have undergone the study, randomely distributed into two groups: one (group E) includes 25 women, was given Misoprostol (PGE1), the other one (group P) consists of 25 women, was given placebo. And as a result, the sample size can be calculated; being accepted when the power reaches from 85 to 100%, so that the beta error *(type II error*) would be less than 0.15. Using the two groups shows that 60 women given the intervention in addition to 60 controls given placebo; 0 out of 60 of group E and 16 out of 60 of group P show decreased neonatal respiratory morbidity. The calculated power of the test equal 99%. At this value; (using a two-sided binomial test with a confidence level of 95%), alpha error is 5% and the beta error is 1%. Thus, 60 patients for each group were considered sufficient for such data types.

Inclusion Criteria

1) Age: 18 years or more.
2) Term singleton pregnancy (38 – 38 $^{+6}$ weeks gestation).
3) Planned for elective transverse lower segment caesarean section.
4) Written informed consent signed by the participating women.

Exclusion Criteria

1) Women with history of significant cardiac disease, eclampsia, pre eclampsia, epilepsy, severe asthma, severe allergic condition.
2) Women with contraindication to prostaglandins as Glucoma or known hypersensitivity to prostaglandins or specifically for Misoprostol.
3) Psychological problem or mental disease that renders the patient not able to understand the nature, scope, and sequences of the study.
4) Pregnancies with known fetal malformations or chromosomal aberration.

METHODS

i. Initial Approach

The participants was approached around the 36th week of gestation, those fulfilling the inclusion criteria was given a handout information leaflet explaining the study details and its aim in Arabic from the trained participating personnel and then those willing to participate in the study were asked to sign written informed consents if agreed upon to be documented .

ii. Detailed history taking and thorough clinical examination

In the first visit planned, all women was underwent full clinical examination after obtaining complete medical history from them. As a result, we had a case record form (CRF1) and an interventional record (CRF2).

In the CRF1 the following data are to be recorded

- Patient initials.
- Patient number according to the schedule of randomization.
- Age, height, weight, body mass index (BMI).
- Medical and surgical history, and any concomitant illness.
- Parity, GA.
- Previous caesarean section.
- Drugs taken in the last month even if discontinued.
- Known allergies or any previous hypersensitivity reaction.
- Clinical examination including general examination, with pulse and blood pressure recording, and local obstetric examination.
- Time from administration of the pessary to delivery of the fetus.
- Type of anesthesia used.

The Interventional record (case record form 2)

After preparing for ECS, vital signs assessed, the intervention given whether containing the Misoprostol medication or placebo according to randomization, timing of administration is recorded, care the women taken in the operating room, and the anesthetic and surgical techniques will be standardized.

Regarding the anesthesia, spinal anesthesia is to be used with preload of 500ml crystalloids and continuation of the intravenous fluid and blood loss replacement.

Regarding the surgical procedure, it was done according to the standard at ASUMH including deferred cord clamping or its milking, the caesarian section and suturing is continued as standard and managed as appropriate to the surgeon with continuous monitoring of vital signs and documentation of any abnormality.

The study reports the neonatal outcome regarding the respiratory distress (suspected when grunting, retractions, hypoxia, or cyanosis immediately after birth), transient tachypnea of the newborn (suspected when increasing the respiratory rate, increasing oxygen requirements, respiratory fatigue within the first few hours after birth), other respiratory morbidities as RDS or PPHN, admission to the neonatal ICU, the length of stay in it, the need for mechanical ventilation, any maternal or neonatal adverse event or mortality.

iii. Intervention

Misoprostol (PGE1) containing vaginal tablet wasin the form of Cytotec vaginal tablet containing 200mcg Misoprostol (manufactured by Pfizer Limited Pharmaceutical Industries, Kent, United Kingdom) will be administered about 60 minutes before scheduled caesarean section. Placebo were given in the form of non Prostaglandin E1medicated vaginal tab. containing only the inactive ingredients (Hydrogenated castor oil, Microcrystalline cellulose, Sodium starch glycolate type A, Hypromellose) which was synthesized with the help of laboratories of Ain Shams Faculty of Pharmacy to be administered vaginally for the purpose of research. The results from all the study population were recorded with coded numbers, for independent cytological assessment to avoid bias in reporting results.

Minimization of bias

1) Observer bias

The study is a double blinded one in which participants, caregivers, personnel, and outcome assessors were blinded till the study end (computer based randomization table).

2) Attrition bias

The intervention will be carried out about an hour before elective caesarean and the follow up is to be done while the mothers, their

neonates are still in the hospital, so significant attrition is not expected.

Outcome measures

Primary outcome

Reduction of incidence of neonatal respiratory morbidities and especially the transient tachypnea of newborn.

Secondary outcome

1. Any adverse event noticed either to the mother or the neonate.
2. Need of neonates for admission into the neonatal intensive care unit.
3. Fetal mortality in the study population.

The study was done after approval of ethical board of Ain Shams university and an informed written consent was taken from each participant in the study.

Statistical Methods

Data collection

All analysis are done according to the principle of the intention-to-treat. Data will be gathered, coded, and tabulated using excel 2007 (Microsoft, Redmond, WA, USA).

Statistical analysis

IBM SPSS statistics (V. 24.0, IBM Corp., USA, 2016) was used for data analysis. Data were expressed as Mean ± SD for quantitative parametric measures in addition to both number and percentage for categorized data.

The following tests were done:

1. Comparison between two independent mean groups for parametric data using Student t test.

2. Chi-square test is used to study the association between each 2 variables or comparison between 2 independent groups as regards the categorized data.

The probability of error (P value) at 0.05 was considered significant (S), while at 0.01 and 0.001 are highly significant (HS), and if more than 0.05 it is considered to be non significant (NS).

RESULTS

This study was conducted at ASUMH starting from November 2016 to April 2017. The study was a Randomized Controlled Trial (RCT), included 120 women planned for caesarean section in order to evaluate the effect of giving prostaglandin E1 versus placebo (group E given "Cytotec" the intervention vaginal tab. containing Misoprostol and group P given the placebo vaginal tab.) 1 hour before delivery on decreasing the neonatal respiratory morbidities. Statistical significance represented as; S: Significant, NS: Non Significant**,** HS: Highly Significant.

Characteristics of the studied population

No statistically significant difference between the two groups regarding the baseline characteristics (age, weight, parity, number and type of previous deliveries, history of abortions, medical history, and surgical history) of the study population

Neonatal outcomes

There is a statistically significant difference between the intervention group and the placebo one regarding the Apgar Score at 1, 5 minutes, respiratory morbidities in general, Transient Tachypnea of the Newborn as an important subtype, NICU admission favoring the use of Misoprostol before scheduled caesarean section by about one hour. There is also a clinically significant difference regarding the neonatal mortality as it concerns mothers the most regardless being of no statistical significance. The following tables illustrate these results in details.

Table (1): comparison between groups according to Apgar Score at one or five minutes.

	The study groups	N	mean	SD	T	p	Sig
Ap. Score 1	Group P	60	6.55	0.649	-2.452	0.016	S
	Group E	60	6.78	0.666			
Ap. Score 5	Group P	60	8.9	0.656	2.619	<0.001	HS
	Group E	60	9.2	0.684			

Ap score 1: Apgar score at 1minute, AP score 5: Apgar score at 5 minutes.

This shows a statistically significant difference between groups according to Apgar score 1 and 5 , using Independent Sample t-test, with p-value <0.05 (S) and <0.001 (HS).

Table (2): comparison between groups according to type of respiratory morbidity

		Placebo	Cases	Total	
Type of respiratory morbidity	**No**	**Count**	44	60	104
		%	73.3%	100.0%	86.7%
	Pneumonia	**Count**	2	0	2
		%	3.3%	0.0%	1.7%
	RDS	**Count**	1	0	1
		%	1.7%	0.0%	0.8%
	TTN	**Count**	13	0	13
		%	21.7%	0.0%	10.8%
Total		**Count**	60	60	120
		%	100.0%	100.0%	100.0%
Pearson Chi-Square	**Value**	18.462			
	p	0.000 **(HS)**			

RDS: Respiratory distress syndrome, TTN: Transient tachypnea of the newborn.

This shows a highly statistically significant difference between groups according to type of respiratory morbidity, including TTN, RDS, pneumonia using Chi-square test, with p-value <0.001 (HS).

Table (3): comparison between groups according to NICU admission

			The study groups		Total
			Group P	**Group E**	
NICU admission	**MV 2D**	**Count**	2	0	2
		%	3.3%	0.0%	1.7%
	MV 6D	**Count**	1	0	1
		%	1.7%	0.0%	0.8%
	N 1D	**Count**	9	0	9
		%	15.0%	0.0%	7.5%
	N 2D	**Count**	3	0	3
		%	5.0%	0.0%	2.5%
	N 3D	**Count**	1	0	1
		%	1.7%	0.0%	0.8%
	No	**Count**	44	60	104
		%	73.3%	100.0%	86.7%
Total		**Count**	60	60	120
		%	100.0%	100.0%	100.0%
Pearson Chi-Square		**Value**	18.462		
		P	<0.001 **(HS)**		

MV: Mechanical Ventilation, N: Nasal tube, D: Days.

This shows a highly statistically significant difference between groups according to NICU days of admission, nasal ventilation, mechanical ventilation using Chi-square test, with p-value <0.001 (HS).

Table (4): comparison between groups according to fetal mortality

			The study groups		Total
			Group P	**Group E**	
Fetal Mortality (FM)	FM	**Count**	2	0	2
		%	3.3%	0.0%	1.7%
	No	**Count**	58	60	118
		%	96.7%	100.0%	98.3%
Total		**Count**	60	60	120
		%	100.0%	100.0%	100.0%

Pearson Chi-Square	**Value**	2.034
	P	0.154 **(NS)**

This shows no statistically significant difference between groups according to fetal mortality, using Chi-square test, with p-value >0.05 (NS).Despite there is no statistically significant difference between the two groups regarding the fetal mortality, it is considered to be of high clinical significance.

DISCUSSION

Prostaglandins are substances that have been successfully used for labour induction in the pregnant females. It is found also to be helpful enabling the neonatal lungs of term newborns to adapt to breathing the room air following labour, by allowing lungs' fluid to be absorped and increasing the secretion of the surfactant as the beta receptors increase in lung towards term [(4)], so the catecholamine surge [(12,13)] that happens after prostaglandin administration stimulates surfactant release [(4)] as a simulation of vaginal delivery which has 7 times less neonatal respiratory diseases rate [(8)].

Respiratory morbidity in neonates is a common birth sequele that concern mothers. They occur more frequently following caesarean section than in vaginal delivery in which the labour stress increase the level of cortisone in maternal blood and level of maternal and thus fetal catecholamines and also squeezing the fetal chest while passing in maternal passages play an important role in that. It is found to happen more when the pregnant females are operated on before the onset of labour as ECS on maternal request than when she is in labour [(12)].

Caesarean sections are frequently done worldwide and it is important to search out interventions that improve the newborn's respiration following it and especially when before an elective caesarean section on term pregnancies to overcome neonatal respiratory morbidity which are Transient tachypnea of newborn (TTN), Respiratory Distress Syndrome (RDS), Persistent Pulmonary Hypertension (PPH) and their future sequele [(8)].

Some studies in animals have demonstrated the effects of catecholamines on fetal lung adaptation to extra-uterine life: One study with a result of Prostaglandin E2 integrates the effects of fluid distension and glucocorticoid on lung maturation [(13)], another provided a study for Prophylaxis of respiratory distress syndrome in premature calves by administration of dexamethasone or a prostaglandin F2 alpha analogue to their dams before parturition [(14)]. Singh performed a randomized controlled trial on thirty six mothers were randomly allocated to receive either 2 mg intravaginal prostaglandin E2 gel (study group; n = 18) or an equal volume of K-Y jelly as a placebo (control group; n = 18) 60 minutes before the ECS and measured the Catecholamine concentrations in the umbilical arterial blood samples collected at delivery [(10)] .It revealed that Noradrenaline (Norepinephrine) concentrations in the umbilical arterial blood were significantly higher in the study while there is no big difference regarding the adrenaline level nor the arterial and venous PH measurments in the study groups with the final conclusion that a labour related catecholamine surge could be simulated by intravaginal prostaglandin E2 gel. But, this study was of a small sample size, and the results are of no clinical significance. There was a difference regarding the respiratory morbidity (one neonate developed TTN in the control group compared to none of the intervention one) which is not statistically significant and there was no difference regarding the NICU admission, or neonatal mortality [(7)]. We found no other reviews, trials or observational studies in the Cochrane review in humans involving the use of prostaglandins for the purpose of improving neonatal respiratory outcomes [(11)].

In our randomized placebo controlled trial we performed a similar trial on a larger sample using PGE1 instead of PGE2 to have the same benefit through simulation normal labour in addition, and being performed upon a larger sample size 120 pregnant women (60 given PGE1, 60 given placebo as a control group) about 1hour before elective caesarean section. The Apgar score was better in the intervention group, either at 1or 5 minutes, respiratory morbidities especially the TTN were prevented, NICU admission and the need for mechanical ventilation were reduced, Fetal mortality from respiratory causes were prevented. But, we did not measure the neonatal PH, nor the Catecholamines concentration in their umbilical cord arterial blood which are of high laboratory and research value despite of being of a little clinical importance as our main aim is to improve the neonatal clinical health outcome.

CONCLUSION

The study concluded that when a vaginal tab containing Misoprostol 200 microgram given to women one hour before term elective caesarean section between $38\text{-}38^{+6}$

weeks compared to placebo, it simulates the normal labour to enable the neonate through catecholamines surge, and thus surfactant secretion for better adaptation to the extrauterine life.

RECOMMENDATIONS

- Misoprostol can be administered vaginally to candidate pregnant women with term pregnancies before an ECS (after exclusion of any contraindication and thorough good history taking and clinical examination) in order to reduce the neonatal respiratory morbidity and especially the transient tachypnea of newborn. Thus, decrease the duration of neonatal NICU admission and mortality.
- Further studies evaluating the effect of PGE1 upon the neonatal respiratory outcome (which concern mothers the most) are required to be used on large scale till it become approved to be used as a routine for a better neonatal outcome and mothers satisfaction.

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