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Changes in Biophysical Parameters and Fetoplacental Circulation After Maternal Betamethasone Administration: A Prospective Observational Study

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KEYWORDS
Antenatal corticosteroid, biophysical profile, fetal hypoxemia, pulsatility index, preterm

ABSTRACT:
Introduction-Antenatal corticosteroids are administered to all antenatal women with threatened preterm labor to avoid respiratory distress syndrome (RDS) because of insufficient surfactant production by immature alveolar pneumocytes. But corticosteroid have certain side effects like transient fetal hypoxemia which may be perceived as signs of fetal distress warranting a preterm birth.
Objective & method- We planned a prospective observational study to study these hypoxemic changes produce by antenatal corticosteroids in 156 patients of threatened preterm labor, by observing biophysical profile (BPP) and umbilical and middle cerebral artery pulsatility index (PI), before corticosteroid administration and 4, 8 and 24 hours, and 3 days after it, till the changes revert back to normal.
Results- It was observed that there was a significant decrease in biophysical profile 4 to 8 hours after receiving betamethasone. However, all these changes reversed to normal values within 3 days. The pulsatility index of umbilical and middle cerebral artery after betamethasone administration significantly reduced after 4 hours whereas the changes seen after that were not significant and came to normal after 24 hours. Out of total 156 patients who had transient signs of hypoxemia, 132 (84.61%) could reach term gestational, because of close monitoring & awareness of transient nature of hypoxemic effects
Conclusion-Study emphasizes the need of understanding the pattern of changes in BPP and doppler studies after corticosteroid administration to prevent unnecessary iatrogenic delivery of preterm fetus.

INTRODUCTION

Antenatal corticosteroid is administered in all threatened spontaneous preterm labor or medically indicated preterm delivery with unknown fetal lung maturity status as well as in those with documented pulmonary immaturity (surfactant/albumin ratio<55), after 28 weeks of gestation.
Preterm labor is defined as onset of labor after 28 weeks & prior to completion of 37 weeks of gestation. Preterm birth is further classified based on gestational age into extremely preterm < 28 weeks of gestation, very preterm 28–32 weeks, and moderate to late preterm, from 32 to 37 weeks of gestation.
The obstetric indications leading to preterm birth, whether vaginal delivery or cesarean section (CS), are, fetal growth restriction or severe preeclampsia, spontaneous preterm labor with intact membranes, preterm rupture of membranes (PROM) and preterm premature rupture of the membranes (PPROM).[1] In India the prevalence of preterm birth is about 5-18% and is a major contributor to neonatal morbidity and mortality, accounting for 70% of neonatal deaths and 50% of long-term complications, including respiratory distress syndrome (RDS) [2,3]
RDS is mainly due to immature lungs & insufficient surfactant production affecting surface tension of alveoli, leading to poor gas exchange, hypoxia & risk of respiratory failure. Successful development and functioning of lungs require both physical development as well as biochemical development. From 17 to 25 weeks of gestation, the bronchial airways grow, widen and lengthen with canalization. The primitive alveoli also known as terminal sacs arise from the enlargement

Journal of Chemical Health Risks
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of terminal bronchioles. These are the functional units of the lung or respiratory lobules. Type I and II pneumocytes develop in the alveoli & are responsible for surfactant production. Number of alveoli & pneumocytes, and their surfactant production increases fourfold between 29 weeks and term, and continue to grow for about one to two years after birth. However, in case of infants born preterm, the number of alveoli is low and hence contribute to respiratory distress syndrome.

Surfactant is needed to decrease the surface tension when breathing out, to prevent collapse of the alveoli. Premature infants are predisposed to RDS which is mainly due to qualitative and quantitative deficiency of surfactant. Another factor responsible for RDS is capillary leakage allowing inhibitors from plasma to reach alveoli which in turn inactivate any surfactant that is present in alveoli. Further, hypoxia, acidosis and hypothermia which are commonly seen in preterm infants can reduce surfactant synthesis required to replenish surfactant lost from the system.

Antenatal corticosteroid administration is the main line of treatment given to women at risk of preterm birth to improve fetal lung surfactant production and enhance fetal lung maturity to reduce the chances of RDS. A 50 % reduction is seen in the incidence of RDS following administration of antenatal corticosteroids, as well as other complications such as severe intraventricular hemorrhage and necrotizing enterocolitis [4, 5].

The standard regimen of antenatal corticosteroids involves either 12 mg betamethasone administered intramuscularly, repeated once after 24 hours or four doses of 6 mg dexamethasone administered intramuscularly every 4 hours. The full effect of antenatal betamethasone corticosteroids is reached 48 h after first administration of the second dose. [6] A repeat single dose (rescue course) can be safely administered up to 34 weeks of gestation, with a minimal interval of 2 weeks from the first course.

Although antenatal administration of glucocorticoids improves neonatal outcome, it has several well-known short-term and long-term effects on both mother and fetus. [7] Mothers are at increased risk of infections such as pyelonephritis, pneumonia, chorioamnionitis and endometritis, treated with multiple doses of corticosteroids due to their immunosuppressive action. [8] There is also a transient increase seen in neutrophil and lymphocytic counts which return to normal values after three days of corticosteroid administration. [9] Another metabolic effect seen in pregnant women after corticosteroid administration is change in glucose metabolism. There is an increase in fasting glucose levels in maternal plasma more than 90 mg/dl for about 5 days after administration of second dose. However, no significant changes occur in mean post prandial glucose. Reduction in maternal cortisol level and maternal plasma adrenocorticotrophic hormone is also observed after treatment with corticosteroid. All these changes are transient and values return to normal after few days.

Studies have shown that pregnant patients treated with corticosteroids develop transient changes of fetal hypoxemia which can lead to over diagnosis of fetal distress and unnecessary iatrogenic delivery, and hence the advantages of improved maturation are offset by the risks of iatrogenic preterm delivery.

The practice of using corticosteroids in preterm labor for achieving fetal lung maturity is conventional throughout the world, but their adverse effects are understudied, not well understood and frequently ignored in the presence of their advantages. Therefore, there is a need to study the pattern of these adverse effects to prevent the complications commonly associated with preterm birth.

Hence a prospective study was designed to study these hypoxemic changes through biophysical profile and doppler velocimetry, and duration of these effects, to prevent unnecessary iatrogenic preterm delivery and thereby preventing the short- and long-term consequences of preterm birth.

OBJECTIVES

The objective of the study was to evaluate the effects of maternal betamethasone, given for insufficient surfactant lungs of preterm fetuses, on the ultrasonographic biophysical profile and doppler velocimetry of umbilical arteries and middle cerebral artery of foetus, their timing of onset and reversal of these changes.

METHOD:

This was a hospital based prospective observational study, carried out in Obstetrics and gynecology department of Mahatma Gandhi Medical College & Hospital, Jaipur, over a period of one year. Institute Ethics Committee approval was obtained before start of

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JCHR (2025) 15(4), 1773-1781 | ISSN:2251-6727

study and before enrolment into the study written and inform consent was obtained from all participants.

Taking the prevalence of preterm birth in India to be 13.3 % [10] and the absolute error of 5%, the sample size came out to be 185. Taking 10% attrition, around 200 patients were to be included in the study. A few patients opted out of study after betamethasone administration, or lost to follow up & in a few ultrasonographic records could not be saved, hence the study was completed using data of 156 patients.

All singleton pregnancies with gestational age from 28-34 weeks and at risk of preterm birth were included in the study. Those excluded were the patients in active labour or those who required immediate delivery, who had already received corticosteroids in their pregnancy, if they already had doppler changes in their sonography, women who had any contraindication of corticosteroid administration, women with PROM or those who had active intrauterine infection, and patients who did not give consent to participate in the study were also excluded.

All eligible patients were admitted, detailed demographic and epidemiological characteristics, medical and obstetric history was taken and complete general physical and obstetrical examination was done.

Gestational age was calculated based on the last menstrual period and confirmed with first trimester crown rump length. The patients were divided into categories according to their gestational age as extremely preterm (≤ 27±6 weeks), very preterm (28-31+6 weeks), moderate (32-33+6 weeks), or late (34-36+6 weeks) preterm.

After checking routine blood investigations for antenatal care including viral markers, cardiotocography was recorded and a baseline ultrasonography was done using Siemens Acuson X300 machine, which included both biophysical profile as well as doppler study. The biophysical profile included all parameters such as fetal breathing movements, fetal tone, fetal limb movements, fetal heart rate variability and amniotic fluid index, and their values were recorded in a tabulated form. The Doppler study of the fetus included study of umbilical artery and middle cerebral artery and calculation of their PI and this too were tabulated.

This was followed by administration of Injection Betamethasone 12 mg intramuscular for 2 doses, 24 hours apart. After administration of second dose of betamethasone, a repeat ultrasonography as well as doppler study were done at 4 hours, 8 hours,24 hours and 3 days. The fetal heart rate, BPP score and PI of both umbilical and middle cerebral arteries were recorded and compared to that of values before administration of betamethasone and their normal range for that gestational age. Changes in relation to time and their reversal to normal were also recorded. In case of changes that are abnormal and persisted beyond twenty-four hours, immediate intervention was done according to the standard obstetric protocol. The data was entered in Microsoft office excel worksheet, appropriate tests were used to find the significant association. A p value of <0.05 was considered statistically significant.

OBSERVATIONS AND RESULTS

Table 1 shows the demographic details of patients, out of total 156 patients, most of the them were between 21-30 years of age (70.5%), those from rural area (55.7%) were more than that of urban population (44.2%) & most of the patients belonged to the moderate preterm category with incidence of 46.7%. multigravida were slightly more (55.7%) than primigravida (44.2%)

Total biophysical profile and their mean were calculated as shown in table 2 and figure 1, & it revealed a significant decrease in biophysical profile 4 & 8 hours after receiving betamethasone. However, all these changes reversed to normal values after 3 days. We observed that fetal heart rate and breathing movements were affected significantly after 4hours and 8 hours but reverted to normal within 3 days, but Fetal tone & AFI did not show any change after betamethasone administration to mother.

Table 3 depicts changes seen in pulsatility index of umbilical artery after betamethasone administration which was significantly reduced after 4 hours whereas the changes seen after that were not significant. Table 4 shows the decrease seen in middle cerebral artery PI which is highly significant after 4, 8 and 24 hours of betamethasone administration

Figure 2 shows a combined uterine artery and middle cerebral artery PI in relation to time since corticosteroid administration, 7 it is clearly evident that there were significant changes up to 24 hours but they revert to normal within 3 days.

As shown in figure 3, that out of total 156 patients, only 24 (15.38%) patients delivered preterm while 132

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JCHR (2025) 15(4), 1773-1781 | ISSN:2251-6727

(84.61%) could reach term before delivery. Of the patients that delivered preterm, 16 (10.25%) had vaginal delivery while 8 (5.12%) had caesarean section. However, patients who had term delivery, 88 (56.41%) had vaginal delivery whereas 44 (28.2%) had caesarean section. These figures emphasize the fact that understanding of hypoxemia changes and their time of reversal can result in taking the patients to term and hence decreasing the perinatal morbidity mortality.

The figure 4 shows that the neonatal complications were very less. Out of total new born, both term and preterm, maximum had no complications that is 114 (73.07%), while 20 (12.82%) fetus developed Jaundice, 10 (6.41%) fetus had respiratory distress syndrome, 7 (4/48%) fetus developed neonatal hypoglycemia and 5 (3.2%) fetus had meconium aspiration syndrome.

DISCUSSION

In patients of threatened preterm labor, corticosteroids were administered in recommended doses to avoid RDS, & the effect of corticosteroids on BPP & doppler velocimetry of fetus were studied.

The mean age of patients in our study was 25.7 years with a standard deviation of 5.6. The mean age of patients in study by Choudhary et al [11] was 25 years, in Taghavi et al [12] was 26.2 years and in Tehrani et al [13] , it was 26.5 years. These studies are indicative that the probability of threatened preterm birth is common in younger age groups.

The mean gestational age of patients included in our study was 32.4 weeks with a standard deviation of 1.5. A study conducted by Gaur et al [14] had a mean gestational age of 33.5 weeks while that by Edwards et al [15] had a mean gestational age 28.5 weeks. Tehrani et al [13] showed a mean gestational age of 32 weeks, Choudhary et al [11] with mean gestational age of 31.58 weeks and Taghavi et al [12] had mean gestational age of 32 weeks.

In our study, transient but reversible changes were seen in fetal breathing movements, fetal movements and fetal heart rate variability. These changes were observed after the second dose of betamethasone and was most pronounced after four hours of the second dose. However, no changes were observed in amniotic fluid index and fetal tone.

These results were consistent with the study conducted by Mulder et al [16] in which betamethasone administration was associated with significant decrease in basal fetal heart rate, long term and short-term variability and body & breathing movements on day 2 and day 3 of the last dose. Another study by Lunshof et al [17] showed a significant decrease in basal fetal heart rate six to twelve hours after first dose, whereas fetal heart rate variability (both long term and short term) and acceleration increased gradually during the first twelve hours, reaching a maximum change at six to twelve hours after betamethasone injection.

Studies have shown that the reduction in body movements resulted from a betamethasone-induced effect on the ultradian rest-activity cycle as indicated by an increase in fetal quiescence and prolonged episodes of uninterrupted rest. [18, 19] The reduction in FHR is secondary to a betamethasone-induced increase in fetal blood pressure triggered by the baroreceptor reflex. The behavioral effects of betamethasone and its effect on Fetal heart rate variability is also the result of glucocorticoid receptor– mediated processes in brainstem nuclei that control the alternation between episodes of fetal rest and activity. [20]

Apart from the biophysical profile of the fetuses, changes were also observed in doppler velocimetry, which were observed by studying the PI of fetal umbilical and middle cerebral artery. Our study showed a significant decrease in umbilical artery PI after four hours of second dose administration of betamethasone. However, no significant decrease was seen at eight or twenty-four hours and the values returned to pretreatment values after 3 days. A similar pattern was observed in the Doppler study of middle cerebral artery which showed significant decrease in pulsatility index at four, eight and twenty-four hours after betamethasone administration. A study done by Taghavi et al [12] to see the changes in umbilical artery doppler after betamethasone administration revealed that betamethasone elicited a statistically significant reduction in umbilical artery PI, after twenty-four hours. This change remained significant up to forty-eight hours, however no change was observed after seventy-two hours.

In the study done by Vafaei et al [21] it was found that there was a significant decrease in umbilical artery PI and a slight increase in middle cerebral artery PI while all the other indices remained same, Study done by Thuring et al [22] showed a significant decrease in PI of umbilical artery and ductus venosus while no change was observed in middle cerebral arteries. These changes

Journal of Chemical Health Risks
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JCHR (2025) 15(4), 1773-1781 | ISSN:2251-6727

were observed two days after betamethasone administration and returned to pretreatment waveforms after four days.

Choudhary et al [11] did a study to study the Doppler changes after maternal betamethasone administration and found that there was a significant reduction in pulsatility index and S/D ratio of umbilical artery, middle cerebral artery and ductus venosus on day two. It was also observed that there was a significant increase in mean umbilical artery PI and mean S/D ratio from day two to day four. However, in case of middle cerebral artery after a statistically significant fall in mean PI and mean S/D ratio, a statistically significant rise was also seen from day two to day four, however the values observed between day zero and day four were found to be insignificant.

A systemic review done was by Mousavi et al [23] to evaluate the alterations in fetal circulation after corticosteroid administration. The study revealed that there was reversible decrease in umbilical artery PI and middle cerebral PI after corticosteroid administration. Similar to our study significant reduction in umbilical artery PI and middle cerebral artery PI were seen in majority of the studies included in the meta-analysis

These changes are mostly due to the relationship of corticosteroids with corticotrophin releasing hormone (CRH). Exogenous corticosteroid decreases CRH secretion from hypothalamus, while increasing secretion of CRH from placenta. Thus, causing betamethasone dependent vasodilation in fetal vessels and reducing pulsatality index. [24]

With these changes observed through our study fetal surveillance after betamethasone administration becomes essential, especially in high-risk pregnancies. These suppressive changes found in biophysical profile can be taken as a sign of fetal compromise but due to the transient nature of these described changes along with changes observed in doppler velocimetry, the possibility of fetal hypoxia can be ruled out. Therefore, it becomes necessary to assess these trends in fetal heart rate variability, breathing movements, fetal movements and doppler changes in patients who are administered betamethasone as knowledge regarding both changes in biophysical profile as well as fetoplacental vasculature and its effect on fetal diurnal rhythm provides helps us prevent unnecessary iatrogenic intervention which might have morbid outcomes for the fetus.

CONCLUSION:

Antenatal corticosteroid administration is the main line of treatment given to women at risk of preterm birth to improve fetal lung surfactant production and enhance fetal lung maturity to reduce the chances of respiratory distress syndrome. However, in our study we found that antenatal betamethasone administration causes significant changes in both biophysical profile and doppler velocimetry such as suppression of fetal breathing movements, fetal movements and fetal heart rate variability after second dose of betamethasone. These changes were most significant after four and eight hours of second dose of betamethasone. No changes were found in fetal tone and amniotic fluid index. Doppler studies revealed a significant decrease in Umbilical artery PI and middle cerebral artery PI after four and eight hours of betamethasone administration. Like the changes of biophysical profile which were seen after betamethasone administration, the changes observed in doppler velocimetry were also seen as early as 4 hours after the second dose of betamethasone administration, maximum up to 8 hours, and most cases showed these changes up to 24 hours. These changes reverted back to pre-corticosteroid values about 3 days after betamethasone administration.

The changes, though transient, in biophysical profile & vessel doppler studies of the fetus can be interpreted as a sign of fetal compromise, however proper monitoring of patients who are administered betamethasone and awareness regarding pharmacologic effect of betamethasone can be helpful in preventing unnecessary iatrogenic delivery of preterm fetus.OBSERVATIONS AND RESULTS

Table 1: Demographic details of the patients

Variables	Very Preterm (28-31^{+6} weeks)		Moderate Preterm (32-33^{+6} weeks)		Late Preterm (> 34 weeks)		Total	
	n	%	n	%	n	%	n	%

Journal of Chemical Health Risks
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JCHR (2025) 15(4), 1773-1781 | ISSN:2251-6727

No. of Patients		61	39.1	73	46.7	22	14.1	156	100
Age of Patients	< 20 years	3	1.9	4	2.5	4	2.5	11	7.05
	21 – 30 years	51	32.6	46	29.4	13	8.3	110	70.5
	31 – 40 years	5	3.2	20	12.8	4	2.5	29	18.5
	> 40 years	2	1.2	3	1.9	1	0.06	6	3.8
Residence	Rural	36	23.0	39	25.0	12	7.6	87	55.7
	Urban	25	16.0	34	21.7	10	6.4	69	44.2
Parity	Primigravida	24	15.3	34	21.7	11	7.0	69	44.2
	Multigravida	37	23.7	39	25.0	11	7.0	87	55.7

Table 2: Total biophysical profile score and its change with time

	Mean	**SD**	**p value**
Before betamethasone	10	0.0	No change
After 4 hours	8.7	2.1	**0.00**
After 8 hours	9.1	1.9	**0.00**
After 24 hours	9.8	0.8	**0.0119**
After 3 days	10	0.0	**No change**

Table 3: Umbilical artery PI changes in relation to time after betamethasone administration

	Mean	**SD**	**p value**
Before betamethasone	1.127	0.149	No change
After 4 hours	1.108	0.050	**0.0466**
After 8 hours	1.118	0.049	0.3599
After 24 hours	1.130	0.160	0.5125
After 3 days	1.127	0.148	0.5457

Table 4: Middle cerebral artery PI changes in relation to time after betamethasone administration.

	Mean	**SD**	**p value**
Before betamethasone	1.846	0.185	No change
After 4 hours	1.562	0.186	0.0000
After 8 hours	1.687	0.186	0.0000

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After 24 hours	1.839	0.186	0.0000
After 3 days	1.846	0.185	0.0313

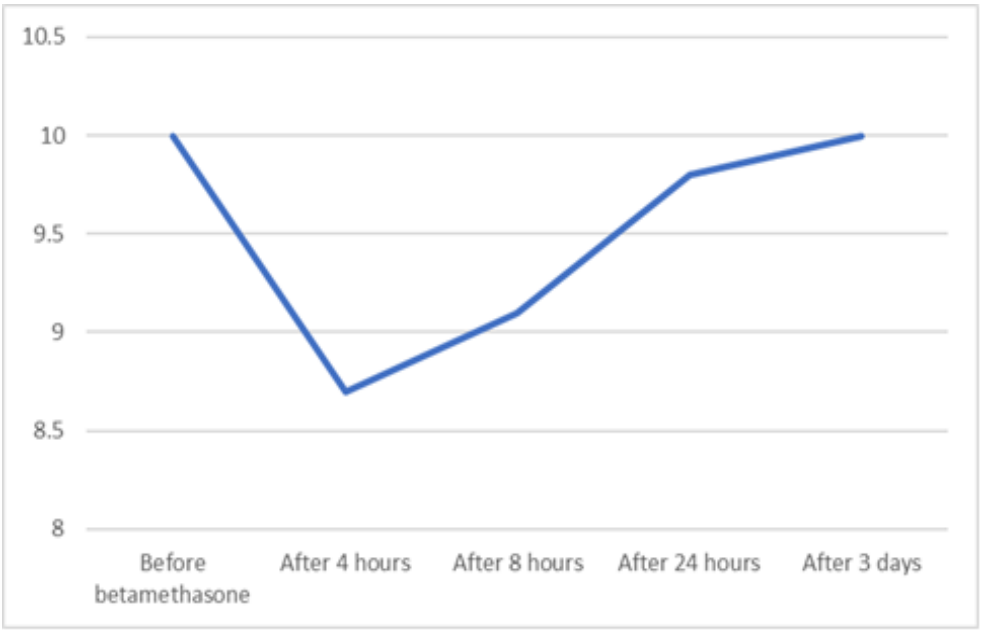

Figure 1: Total biophysical profile score after betamethasone administration in relation to time

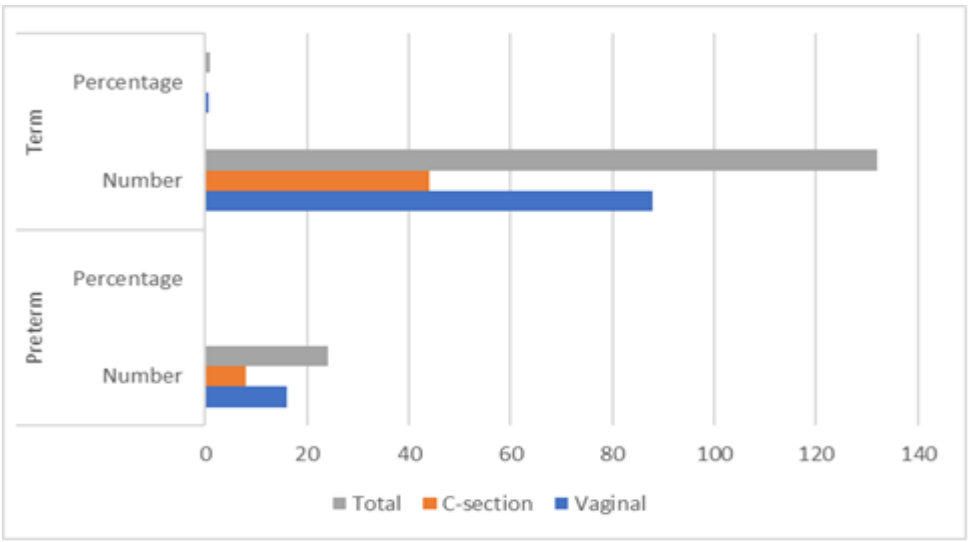

Figure 2: Outcome of Patients in Terms of Gestational Age and Mode of Delivery

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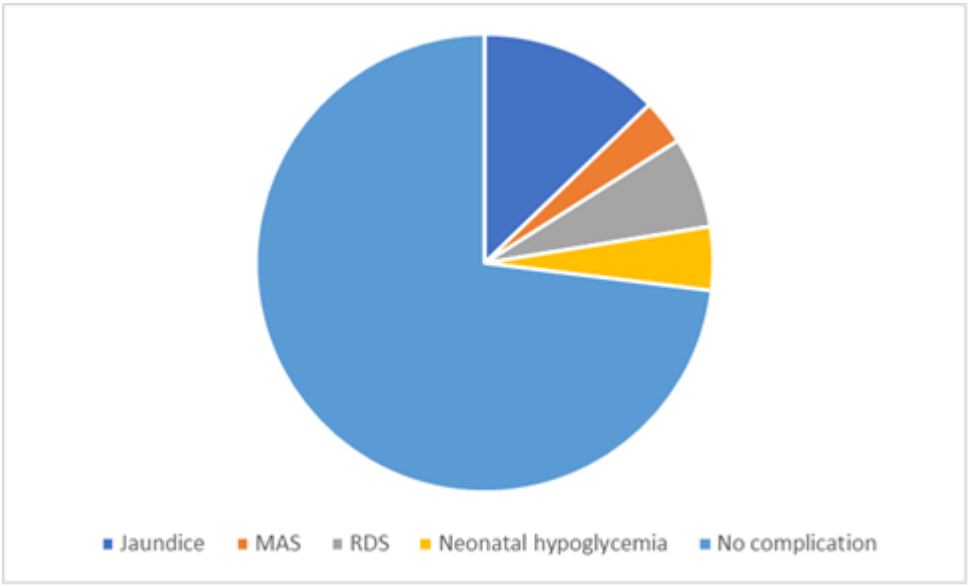

Figure 3: Neonatal Outcome (Both term & preterm)

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