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ORIGINAL ARTICLE

Late preterm infants – impact of perinatal factors on neonatal results. A clinical study

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Abstract

Introduction. Infants born between the 34th – 36th week of pregnancy account for 75% of all preterm infants. Their seemingly slight immaturity is related to serious health problems.

Objective. The aim of the study was to analyse perinatal factors that influence the occurrence in infants of such problems as respiratory failure, metabolic problems and early onset sepsis (EOS).

Materials and method. The material for the study included all mothers and their late preterm infants: 34+0 – 36+6 born in our hospital (a tertiary referral academic centre) in 2010 and 2011. The course of pregnancy and delivery, the type of delivery, applied preventive measures and treatment, as well as demographic data and the clinical state of infants were all analysed. Data from individual documentation of each mother and infant were collected by 5 designated people and data reliability was independently monitored by a random control of the documentation conducted by the supervising person.

Results. A statistically significant relationship between the occurrence of respiratory distress syndrome and infant immaturity, bad state after birth and sepsis in infants were confirmed. Sepsis was more common in the case of vaginal delivery, and coexisted with respiratory distress syndrome. The mother's diseases during pregnancy, a perinatal preventive antibiotic therapy, and possible delivery complications did not influence the infection. Perinatal asphyxia in an infant positively correlated with a Caesarean section and respiratory distress syndrome after birth.

Conclusions. It is necessary to thoroughly establish the type of delivery of a late preterm infant in order to prevent an infection in the newborn child. The improvement of diagnosis of intrauterine hypoxia may reduce the number of Caesarean sections. The decision about late preterm delivery should be based on indices of the mother's state of health. Premature delivery is related to the occurrence of respiratory distress syndrome in a late preterm infant, although the risk is reduced by the application of an antenatal steroid therapy.

Key words

late preterm, perinatal risk factors, respiratory distress syndrome, infection, intrauterine asphyxia

INTRODUCTION

Infants born at 34+0 – 36+6 weeks of gestation are in the group of the so-called 'late preterm infants' (LPI). Other expressions in the literature used to describe this group of children such as 'born before the expected date of delivery' or 'preterm' do not seem to fully express their health problems. In the total population of preterm infants, late preterm infants constitute a big group – 75% [1]. Over the last 30 years, the size of this group of infants has increased by 25% [2]. Literature data indicate an increased occurrence of various health problems, including the increased morbidity and mortality of these children, compared to children born at term [3, 4, 5, 6].

Bearing in mind the indication and emphasis of significant health problems of this age group, an analysis was conducted of risk factors from the period of gestation and delivery, of their interrelations and the influence on the state of health after birth.

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OBJECTIVE

The aim of the study was to indicate which gestation- and delivery-related factors increase the risk of such conditions as perinatal hypoxia, respiratory failure and early onset sepsis in late preterm infants.

The occurrence of inborn developmental disabilities and the frequency of an antenatal steroid therapy were analysed. In the research population of women, the frequency and type of diseases that complicated pregnancy and delivery, as well as the occurrence of disorders and diseases in infants were determined.

MATERIALS AND METHOD

The individual documentation of all patients from the obstetrics ward of the Clinic of Gynaecology and Obstetrics (tertiary referral academic centre) during 2010 – 2011 was analysed, together with the medical history of their children who were delivered between 34 0/7 and 36 6/7 weeks of gestation. Infants referred to our clinic from other hospitals were excluded from the research due to incomplete data.

Information regarding the course of gestation, including mother's diseases, was collected: hypertension, severe pre-eclampsia, diabetes and other sudden conditions that would

pose a threat to the life of a mother, such as eclampsia, haemorrhage caused by pathology of the placenta, infections and colonisation of genital tracts by Streptococcus agalactiae group B (GBS), and the application of an antenatal steroid therapy. Types and courses of deliveries were analysed, including the frequency of preterm premature rupture of membranes and features disturbing the well-being of a foetus, such as placental blood flow disorders or pathology of placentation. The analysis included the state of infants after birth (Apgar score 5 minutes after birth), mass at birth, central nervous system (CNS) haemorrhage, respiratory failure, early onset sepsis, hyperbilirubinaemia, hypothermia and hypoglycaemia.

For the purposes of the study, an electronic data form was created. The list of patients and infants was compiled on the basis of the department register. Individual documentation of mothers and infants was gathered from the hospital archive. Data were collected by a team of 5 trained people. The compatibility of data with the medical records was verified by a Clinical Research Associate. Full compatibility between the list of patients and available medical records was confirmed.

In the analysed period of time the same uniform criteria were applied for the assessment of the gestation age, the diagnosis of preterm premature rupture of membranes (PPROM), the bacteriologic diagnosis of pregnant women, an empiric antibiotic therapy, an antenatal steroid therapy and tocolytic treatment, as well as the qualification for the delivery. The correlation between an infant's maturity and mass at birth was based on the centile rank, which allowed the selection of the so-called small gestational age (SGA) group. During the whole research period the criteria for the diagnosis of early onset sepsis (EOS) and qualification for surfactant application were based on the uniform algorithms of the Neonatology Clinic [7–9].

Methodology and the use of statistics. The aim of the analysis was to find a relationship between factors influencing the foetus during gestation and delivery, and the parameters of foetal well-being, such as: respiratory failure, early onset sepsis, features of perinatal asphyxia (Apgar score, lactates, umbilical cord blood pH).

The factors affecting the foetus during gestation were mother's diseases (diabetes, hypertension, severe pre-eclampsia, eclampsia), GBS colonisation, and antenatal steroid therapy. Factors affecting the foetus during delivery were, among others, the foetal age, asphyxia, pH and the concentration of lactates. All the factors were compared. Depending on the type of scale on which they were measured, the following statistical tools were applied: chi^2, Kendall's τ, the Mann-Whitney U test, the Student's t-test.

Statistical significance was set to α=0.05. The applied statistical tools indicate the existence or lack of relationships, however they do not show their direction.

RESULTS

The study comprised 145 mothers and 184 infants. Complete data in each planned category were acquired from the medical records. The clinical and demographic characteristics of the research group are included in Table 1.

The most common pathology in infants during the hospital stay was hyperbilirubinaemia, which affected approximately a half of the research group. The second most common metabolic disorder – hypoglycaemia – occurred in 30 infants (16%). In 39 infants, inborn developmental disabilities were found, which accounted for 21% of the described group.

Table 1. Infants after delivery. One infant in four after delivery demonstrated symptoms of sepsis that required an antibiotic therapy

Characteristics			Number of patients [%]
Type of pregnancy	singlet		145 [78.80]
	multiple		39 [21.20]
Mother's diseases during pregnancy	hypertension		32 [17.39]
	preeclamptic state /eclampsia		14 [7.60]
	diabetes		16 [8.69]
Type of delivery	Vaginal		60 [32.60]
	CS		124 [67.40]
Antenatal steroid therapy	no		106 [57.60]
	yes		78 [42.39]
GBS colonisation *	Negative		56 [30.43]
	Positive		14 [7.60]
	No results		114 [61.95]
Perinatal antibiotic therapy	no		143
	yes		41 [22.28]
Placenta praevia	no		181
	yes		3 [1.63]
Placental blood flow disorders	no		176
	yes		6 [3.26]
PROM > 18 h	no		162
	yes		22 [11.96]
Threatening asphyxia	no		160
	yes		24 [13.04]
Asphyxia [Apgar score]	none [8-10]		169
	moderate [4-7]		13 [7.07]
	severe [0-3]		2 [1.09]
Maturity [hbd]	34		53 [28.80]
	35		52 [28.26]
	36		79 [42.93]
Body mass [g] *Median: 2480,00 SD: 473,39*	<= 1500		4 [2.17]
	1501-2000		22 [11.97]
	2001-2500		74 [40.22]
	2501-3000		65 [35.33]
	> 3000		19 [10.33]
IUGR**	34 hbd	n= 53	10 *[19.6]*
	35hbd	n= 52	9 *[17.3]*
	36 hbd	n= 79	6 *[7.6]*
	Total	*n=184*	*25 [13.6]*
Length of hospital stay [days] *Average: 9*	< 3		20 *[10.87]*
	3-7		58 *[31.52]*
	8-15		81 *[44.02]*
	16-30		24 *[13.04]*
	> 30		1 *[0.54]*
Discharge	to home		162 *[88.04]*
	To other hospital		22 *[11.96]*

* GBS colonisation – Group B Streptococcus **IUGR – intrauterine growth retardation

Table 2. Perinatal hypoxia

		Number of children n=184
Sepsis in an infant	no	136
	yes	48
Hyperbilirubinaemia	no	101
	yes	83
Hypoglycaemia	no	154
	yes	30
Hypothermia	no	182
	yes	2
Inborn developmental disabilities	no	145
	yes	39
IVH	no	130
	yes	28
	lack of data	26
Neonatological Intensive Care Unit	no	82
	yes	102
Respiratory disorders	none	133
	slight (passive oxygen delivery)	10
	severe (mechanical ventilation)	41
Surfactants after delivery		4
of which after antenatal steroid therapy		3

Table 3. Respiratory distress syndrome

The relationship of birth asphyxia in an infant with:	Type of statistics	Statistical value	p
– the occurrence of sepsis	Mann-Whitney U-test	2966.5	0.286
– the occurrence of hypoglycaemia	Mann-Whitney U-test	2075.5	0.317
– type of delivery	Mann-Whitney U-test	3054.5	< 0.050
– threatening asphyxia	Mann-Whitney U-test	1583.5	0.116
– respiratory disorders	Kendalla's τ	-0.46	< 0.001
– mother's diseases hypertension	Mann-Whitney U-test	2049.5	0.112
– mother's diseases: eclampsia	Mann-Whitney U-test	908.0	0.940
– mother's diseases: diabetes	Mann-Whitney U-test	1267.0	0.667
– GBS colonisation during pregnancy	Mann-Whitney U-test	385.0	0.909
– pH	Kendalla's τ	0.10	0.519
– the level of lactates	Kendalla's τ	-0.21	0.919

Table 4. The antenatal steroid therapy

Maturity [hbd]		34	35	36	P
Antenatal steroid therapy	no	12	31	63	$chi^2 = 43.1$, $p < 0.001$
	yes [%]	41[77.35]	21[39.62]	16[20.25]	
	[n]	53	53	79	

p – statistical significance

102 (55.4%) late preterm infants qualified for referral to the Neonatological Intensive Care Unit due to respiratory and/or circulatory instability, inborn developmental disabilities or significant metabolic disorders that required intensive supervision. Almost every third child from the whole group had respiratory distress syndrome, and mechanical ventilation was necessary in over 80% of cases in this subgroup. Four infants were given surfactant, 3 of whom did not undergo any antenatal steroid therapy. In 15,2% of infants, central nervous system haemorrhage was diagnosed with the use of trans-fontanel ultrasonography (Tab. 2).

The analysis of factors correlating with the occurrence of perinatal asphyxia showed a statistically significant correlation with the type of delivery and the occurrence of respiratory distress syndrome in infants. Children born vaginally had a better Apgar score than children born by Caesarean section ($p < 0.05$). The diagnosis of 'threatening asphyxia' as an indicator for a Caesarean section did not result in a decreased Apgar score. The correlation between the occurrence of perinatal asphyxia and mother's diseases during pregnancy or intrapartum complications was not proved (Tab. 3).

The frequency of an antenatal steroid therapy was higher in the youngest age group (over 77%, in the group 34 hbd), showing a statistically significant difference as compared with groups of higher maturity (Tab. 4).

Immaturity is related to respiratory distress syndrome, statistical significance ($p<0.001$). Sepsis in an infant strongly correlates with respiratory distress syndrome ($p<0.001$). Another statistically significant factor correlating with respiratory distress syndrome is perinatal hypoxia, expressed by Apgar score at the 5th minute of life ($p<0.001$). In the group of infants in whom respiratory distress syndrome occurred, steroids were more often used during the prenatal period ($p=0.058$). Other analysed factors, type of conception (sexual intercourse or assisted reproductive techniques), mother's diseases during pregnancy or a state described as threatening perinatal asphyxia, did not correlate with respiratory distress syndrome in an infant. No significant differences in the frequency of respiratory distress syndrome occurrence were found between the group born by Caesarean section and the group born vaginally (Tab. 5).

Table 5. Sepsis in an infant

The relationship of respiratory failure in an infant with:	Type of statistics	Statistical value	p
– antenatal steroid therapy	chi^2	5,68	0,058
– the occurrence of sepsis	chi^2	30,54	< 0,001
– the occurrence of hypoglycaemia	chi^2	1,09	0,579
– Apgar score at 5'	Kendalla's τ	-0,46	< 0,001
– type of delivery	chi^2	4,32	0,116
– hbd	Kendalla's τ	-0,23	< 0,001
– threatening asphyxia	chi^2	0,18	0,913
– mother's diseases hypertension	chi^2	3,48	0,175
– mother's diseases: eclampsia	chi^2	1,79	0,409
– mother's diseases: diabetes	chi^2	0,97	0,616
– GBS colonisation during pregnancy	chi^2	4,02	0,134
– pH	Kendalla's τ	-0,32	0,072
– the level of lactates	Kendalla's τ	0,17	0,482

Early onset sepsis was diagnosed in 26 late preterm infants. Respiratory distress syndrome positively correlates with sepsis ($p<0.005$). A relationship between the occurrence of EOS and the type of delivery was confirmed. Sepsis more often occurred in children born vaginally than in those born by Caesarean section ($p<0.050$). The application of an antibiotic therapy during the perinatal period positively

correlates with the occurrence of early onset sepsis in an infant (p=0.005).

There was a hypoglycaemia trend in children with EOS (p=0.058). The relationship between the occurrence of sepsis and threatening asphyxia, PPROM > 18h, lowered pH in umbilical blood, Apgar score at the 5th minute of life was proved, any of the mother's diseases during pregnancy and delivery were not proved (Tab. 6).

Table 6. The factors related to the occurrence of sepsis in an infant

The relationship of sepsis in an infant with:	Type of statistics	Statistical value	p*
– the occurrence of hypoglycaemia	chi^2	3.60	0.058
– antenatal steroid therapy	chi^2	0.31	0.575
– Apgar score at 5′	Mann-Whitney U-test	2966.5	0.286
– perinatal antibiotic therapy	chi^2	8.68	< 0.005
– PROM > 18h	chi^2	1.37	0.242
– type of delivery	chi^2	5.17	< 0.050
– threatening asphyxia	chi^2	0.14	0.713
– respiratory failure	chi^2	30.54	< 0.001
– mother's diseases hypertension	chi^2	1.38	0.240
– mother's diseases: eclampsia	chi^2	0.49	0.826
– mother's diseases: diabetes	chi^2	1.18	0.227
– GBS colonisation during pregnancy	chi^2	0.18	0.893
– pH	Student's t-test	1.85	0.079
– the level of lactates	Student's t-test	-1.80	0.143

p – statistical significance

DISCUSSION

Demographic analysis of the last few decades indicates an increase in the percentage of late preterm infants and, at the same time, an improvement in the survival rate, and a simultaneous increase in the percentage of iatrogenic preterm births (IPB). It seems that without iatrogenic preterm deliveries, including late preterm deliveries, there would be an increase in intrauterine mortality. The choice of an optimal date and type of delivery is a compromise between an obstetrician's concern about the state of a pregnant woman's health and well-being of the foetus, and a neonatologist's worries about possible complications of a preterm delivery and respiratory failure. Undoubtedly, indications of early delivery are severe pre-eclamptic state, eclampsia, premature placental abruption, placenta praevia haemorrhage, suspected placenta increta, suspected uterine rupture, intrahepatic cholestasis of pregnancy with a very high increase of bile acids (> 60 micromole/L) and late intrauterine development of the foetus with incorrect or suddenly worsening Doppler flows, or the lack of foetal development in recommended time intervals.

The decision for early delivery may be questionable in the case of stable chronic hypertension, mild pregnancy-induced hypertension, and a mild course of intrahepatic cholestasis of pregnancy, especially with a concentration of bile acids < 40 micromole/L [10].

Potentially, the frequency of premature interventions might be decreased in the case of oligohydramnios, late intrauterine development with monitored well-being of a foetus, in women after a classic Caesarean section, or after myomectomy. However, such situations require in-depth observation and monitoring of the state of a mother and foetus. Symptoms reported by a pregnant woman and test results are sometimes ambiguous, and the demanding attitudes of women and their families sometimes force decisions that are not completely medically justified.

The aim of the presented study was to determine which pregnancy- and birth-related factors increase the risk of health complications in late preterm infants, such as perinatal hypoxia, respiratory failure and sepsis.

The perinatal hypoxia was defined by the Apgar score and complemented by the following tests: pH, deficiency of bases and concentration of lactates in blood taken from the umbilical artery. It should be stressed that the cerebrum in 34–36-week infants is still intensively developing and maturing. H. C. Kinney, in an overview paper on periventricular leukomalacia (PVL), clearly indicates that an infant's cerebrum with 34–36-weeks-long maturity is still immature. Imaging studies on the structure and mass of the cerebrum in late preterm infants (the mass of the cerebrum at the 34th week is only 65% of the mass of the cerebrum in an infant born at term) prove intensive maturity and development processes. The structural immaturity of the brain, unshaped antioxidising mechanisms, and the risk of hypoxia and sepsis lead to the vulnerability of the central nervous system to damage (haemorrhages, PVL) in this age group being still high [11].

In prospective research by Morgan et al. it was proved that differences in parameters of psychomotor development of a late preterm infant (AIMS Alberta Infant Motor Scale and GMDS Griffiths Mental Development Scales), compared with infants born at term, are visible until the 12th month of life. The differences are greater in male infants born by Caesarean section as a result of sudden indications to do so [12].

The presented observations are similar – infants born vaginally were in a generally better state than those born by Caesarean section. At the same time, suspected intrauterine asphyxia was not taken into account – a Caesarean section does not improve the results of treatment. The current study proved that in infants born by Caesarean section because of threatening asphyxia, no symptoms of hypoxia were found. On the one hand, this might be due to a timely intervention; however, on the other hand, it might be the result of over-interpretation of cardiotocography data and assessment of incorrect Doppler flows in the umbilical artery, the middle cerebral artery or the ductus venosus.

In the analysed group of late preterm infants, the perinatal hypoxia, to a statistically significant degree, was related to respiratory distress syndrome. However, it was not proved that the occurrence of perinatal hypoxia was influenced by the analysed mother's diseases during pregnancy or complications during delivery.

The frequency of an antenatal steroid therapy in the analysed group was different, to a statistically significant degree, in particular maturity groups of late preterm infants and in the youngest age group – it was the highest at 34 weeks. The percentage of steroid therapies in the group 36 hbd was the lowest and amounted to 20%. This is very low, bearing in mind that this therapy reduces the frequency and intensity of respiratory distress syndrome (RDS) in infants and other complications related to early delivery. The lack of therapy

in 23% of patients at the 34th week of pregnancy meant that delivery took place before the end of a 24-hour therapy, or there were contraindications for its application.

The reduction of RDS after an antenatal steroid therapy was proved in this study, showing a difference that was almost statistically significant. Immaturity, lowered Apgar score and lowered umbilical blood pH positively correlate with the occurrence of respiratory distress syndrome. This syndrome of pathological symptoms indicates a high risk of the occurrence of health disorders in a prematurely born child. Surfactant was administered to only 4 infants, 3 of whom were given an antenatal steroid therapy. There was no correlation between the occurrence of RDS and the type of delivery, mother's diseases during pregnancy and analysed complications at delivery. On the basis of the presented results, it can be stated that a steroid therapy does not reduce the risk of complications related to the immaturity of infants.

The third of the analysed health problems in infants was early onset sepsis. This is a syndrome in which the symptoms can usually appear until the third day of life and are caused by pathogens from the mother's genital tract. The infection is usually initiated during delivery [7]. The risk of the development of an infection in an infant is especially high if clinical symptoms of chorioamnionitis are diagnosed in the mother. In the case of our neonatology team, the occurrence of this syndrome is the cue to apply a preventive antibiotic therapy in an infant after delivery, regardless of the clinical state of the infant, and even before bacteriological proof of infection [8]. Chorioamnionitis is clinically diagnosed on the basis of increased body temperature above the level of 38 °C in a pregnant woman, her leucocytosis, tachycardia of the foetus, sensitive uterus during palpation or diagnosis of inflammatory features of outflowing amniotic fluid. As is known, these are late symptoms that are revealed with a developed inflammation [13]. They are accompanied by a spontaneous contractile action of the uterus, or when there are no contraindications for vaginal delivery (such as breech presentation) the contractile action is stimulated pharmacologically. Hence, paradoxically, a vaginal delivery of a late preterm infant is connected with more frequent sepsis and respiratory distress syndrome, which was proved in the presented study, and is not observed in children born at term. In research by Puopolo, the majority of infants with diagnosed EOS were born by Caesarean section [14].

The dominating clinical symptom of EOS in late premature infants is respiratory failure. These infants are more often born with biochemical disorders (lowered blood pH taken from the umbilical artery). A correlation between the occurrence of sepsis and complications of pregnancy or delivery, including GBS colonisation or the length of amniotic fluid outflow, has not been found. Especially crucial, and unsurprising in the light of the latest reports, is the association of early onset sepsis in infants with increased antenatal antibiotic therapy. In the group of analysed late preterm infants, an inverse correlation between the application of an antibiotic therapy during the period of delivery and the diagnosis of early onset sepsis in infants was proved. This confirms the statement that antibiotics, applied according to present-day recommendations in women in labour, do not protect an infant from sepsis [15]. The doses of antibiotics used for adults do not guarantee therapeutic concentrations in the amniotic fluid and the placenta.

In the case of PPROM in the group of patients with a maturity of pregnancy of 34–36 weeks, no optimal procedure has been established to-date. In literature there are described cases of prolonging the time of pregnancy to such maturity that allows a child's survival and further optimal development, even if rupture of the membrane takes place before the 22nd week of pregnancy [16]. The review of the Cochrane database does not give grounds for an unequivocal choice of inducing delivery or a wait-and-see attitude in this period of pregnancy [17]. The use of antibiotics with PROM is related to a statistically significant decrease of chorioamnionitis frequency and a drop in premature deliveries. Some of the prevalence rate markers are decreased: sepsis, surfactant administration, the use of oxygen, and incorrect ultrasonography image of the brain [18].

Van der Ham et al. conducted research in 60 hospitals in the Netherlands with the participation of 536 randomised patients, in which the influence of the type of delivery was compared – inducted (prostaglandins, oxytocin or Caesarean section vs. wait-and-see procedure) – on the frequency of early onset sepsis in the group of late premature infants. It was also studied whether a shorter duration of delivery in the case of PPROM affects other results of treatment of a mother and child, and the length of a hospital stay. It was confirmed that the frequency of chorioamnionitis was reduced in the group with induced delivery, but there were other benefits resulting from shorter delivery, including the reduction of sepsis in infants [19]. The American College of Obstetricians and Gynecologists recommends induced delivery [20]. In the case of a wait-and-see procedure with PPROM, in order to prolong the pregnancy and decrease the risk of sepsis and reduce the prevalence of infants related to the gestational age, the administration is recommended of antibiotics antenatally and by mouth for a period of 7 days.

The Royal College of Obstetricians and Gynaecologists allows the wait-and-see attitude to be chosen, bearing in mind the risk of chorioamnionitis growing with time, and with a probably lower risk of respiratory distress syndrome and a stay at a neonatal intensive care unit [21]. In many highly developed countries there are no unified procedure doctrines, and the Polish Gynaecological Society has not stated their position on this subject. The decision about an antibiotic therapy is not an easy one. Short-term benefits (prolonged pregnancy, fewer anomalies in the ultrasonography image of the brain) should be assessed against other benefits, including perinatal mortality and other results.

CONCLUSIONS

With the use of modern obstetrical procedures, the diseases of a pregnant woman, such as hypertension, pre-eclamptic state, diabetes or GBS colonisation, do not significantly influence the state of a late preterm infant.

A therapeutic decision of a perinatology team about a delivery at 34+0 – 36+6 should be mainly concentrated on factors determining the mother's state of health.

The methods for diagnosing threatening intrauterine asphyxia and a related urgent Caesarean section do not reduce the frequency of hypoxia in late preterm infants. It is necessary to improve diagnostics and obstetrical procedures within the scope of predicting foetal hypoxia

on the grounds of medicine based on evidence, and not on subjective assessment and intuition.

An antenatal steroid therapy reduces the frequency of the occurrence of respiratory distress syndrome, though the main factor that determines it is an infant's immaturity.

Early onset sepsis in late preterm infants is related to vaginal delivery – the mechanism initiating delivery may be related to an infection of an ovum.

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