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Timing and dosage of intrapartum prophylactic penicillin for preventing early-onset group B streptococcal disease: assessing maternal and umbilical cord blood concentration

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ABSTRACT

Objective Timing of administration of antibiotics and concentrations in maternal blood and the umbilical cord blood are important prerequisites for optimal intrapartum antibiotic prophylaxis (IAP) of neonatal early-onset group B streptococcus (GBS) disease. This cohort study aimed to explore penicillin concentrations in mothers and infants at birth in relation to time elapsed from administration to delivery and to the minimal inhibitory concentration (MIC) for GBS.

Main outcome measures Penicillin G concentrations in maternal and umbilical cord blood in relation to time and dose from administration to time of delivery.

Results In 44 mother–infant dyads, median maternal penicillin G concentration was 0.2 mg/L (IQR 0–0.8 mg/L; range 0–1.6 mg/L). Median infant penicillin G concentration was 1.2 mg/L (IQR 0.5–5.0 mg/L; range 0–12.7 mg/L). In all infants (N=38) born less than 4 hours after the latest IAP administration, penicillin G concentrations far exceeded MIC (0.125 mg/L), even after short time intervals between IAP administration and birth. The highest plasma concentrations were reached in umbilical cord blood within 1 hour from IAP administration to birth.

For 44 mother–infant dyads, maternal concentrations were very low compared with their infants'; particularly, very high concentrations were seen in the 20 infants with only one dose of IAP.

Conclusion High concentrations of penicillin G were found in umbilical cord blood of infants born less than 4 hours after IAP administration, well above the MIC for GBS.

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ International guidelines outline strategies for administration of intrapartum antibiotic prophylaxis (IAP) to prevent neonatal early-onset group B streptococcus disease (EOGBS) and advice observation of the infants for 48 hours if IAP is given less than 4 hours before delivery.

WHAT THIS STUDY ADDS

⇒ High concentrations of penicillin G were detected in infants born less than 4 hours after the first and only IAP administration.

⇒ Even short intrapartum exposure to penicillin G leads to significant levels in infant's bloodstream well beyond minimal inhibitory concentration for group B streptococcus.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ Just one dose of IAP may be sufficient to consider the preventive measure for EOGBS successful, and it may be inaccurate to consider all infants exposed to less than 4 hours of IAP at risk for EOGBS.

⇒ Further studies are needed to evaluate whether healthy infants exposed to one dose of IAP shortly before birth that were previously hospital bound may be safe to discharge.

⇒ Studies of maternal, fetal and infant plasma concentrations should consider the specific pharmacokinetics during birth, and further studies should compare umbilical cord and infant concentrations of IAP.

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INTRODUCTION

Globally, up to one-third of women in labour receive intrapartum antibiotic prophylaxis (IAP) as a preventive measure against neonatal early-onset group B streptococcus disease (EOGBS).

Despite a decline, EOGBS still affects approximately 230 000 infants worldwide each year and occurs even in populations with vigorous screening and IAP.[1]

International guidelines outline two main strategies for IAP; universal antepartum culture-based group B streptococcus disease (GBS)-screening or intrapartum, risk factor-based screening.[2] Recently, several European hospitals, including most Danish hospitals, have introduced the intrapartum GBS PCR point-of-care testing (POCT) in women with some of the recognised risk factors, for example, a GBS culture positive urine (≥10×4 CFU/mL) during current pregnancy, prolonged rupture of membranes or 35 or 36 weeks gestation at birth of. Then, only PCR-positive women receive IAP.[3–6]

Standard IAP is penicillin G 3 g followed by 1.5 g every 4 hours until delivery.[2] This recommendation originates from a 1996 CDC guideline and

consists of a 4 hourly penicillin G regimen and observation of the infant for at least 48 hours after birth.[7] The penicillin G regimen has been maintained in updates of the guidelines.[8 9] Current risk assessment for infants born at or after 35 weeks implies 36–48 hours of in-hospital observation.[10]

The rationale behind this treatment regimen is to obtain levels of penicillin above the minimal inhibitory concentration (MIC) in the fetal blood stream to prevent EOGBS. The exact dose and timing of penicillin for clinical and particularly preventive efficacy is, however, controversial.[9 11] Unknown factors such as placental transfer, and pharmacokinetics during the latent and active phase of delivery may also influence the concentration in fetal blood. In the neonate, several factors influence the penicillin concentration, including the exceedingly low glomerular filtration rate in the first days after delivery, rapid changes in body composition, neonatal disease, for example, multiorgan hypoxia and ischaemia, and transitional circulatory problems.[12]

The evidence behind current guidelines for IAP on prophylactic doses, dosing interval and duration of penicillin G, is weak.[13]

The available literature indicates that beta-lactam antibiotics administered to the mother as IAP rapidly reach therapeutic levels in the fetal circulation,[11 14] but not many studies have compared the antibiotic plasma concentrations in maternal and umbilical cord blood by the time of IAP administration and delivery.[11 13 15 16] Thus, knowledge gaps regarding the optimal timing and dosing of IAP persist.

This study aimed to explore penicillin G concentrations in mothers and infants that is, umbilical cord blood, at birth in relation to time elapsed between IAP administration and delivery.

METHODS

Between 23 April and 15 November 2020, all women admitted in labour at two Danish hospitals (Aarhus University Hospital and Lillebaelt Hospital) were invited to participate in a study on SARS-CoV-2 during delivery, 1042 participated.[17] A blood sample was drawn from the women shortly before or shortly after delivery, and at the time of cord clamping, a blood sample was also drawn from the umbilical vein.

For 76 women, penicillin G was administered as IAP and these women were included in the present study. For 44 of these 76 women and their infants, the following were available: (1) a maternal blood sample, (2) an umbilical cord sample, (3) time and dose of penicillin G administration, and (4) time of delivery.

Information on maternal characteristics, pregnancy complications, infant characteristics and condition at delivery was retrieved from the electronic medical patient records by cross-referencing mother and infant by use of their unique personal identification number given to all citizens in Denmark at birth. Dose, number of doses and time of administration (hours; minutes) of the last dose were registered. Time of delivery was registered. Cord clamping and sampling from the umbilical vein were performed between 5 and 15 min after delivery. The infusion time for penicillin G was 15–30 min. Maternal samples were taken close to or soon after delivery, but the exact timing of maternal sampling was not available.

Blood samples were stored at +5°C for a maximum of 24 hours. After centrifugation, plasma samples were stored shortly at −20°C and then transferred to −80°C where they were kept until analysis.

The plasma samples were analysed at the accredited hospital laboratory at the Department of Clinical Biochemistry, Aarhus University Hospital, Denmark (DS/EN ISO/IEC 15189).

The unbound plasma concentrations of penicillin G were measured by high-performance liquid chromatography (HPLC) with ultraviolet (UV) detection. The HPLC-UV system consisted of an Agilent Series 1290 HPLC system with a diode array detector (Agilent Technologies, Denmark). Analytical separation was performed on a Poroshell 120 EC-C18 column (2.7 µm, 2.1×100 mm) (Agilent Technologies, Denmark) at a temperature of 40°C (penicillin G) controlled by a column heater. The mobile phases had a flow rate of 0.5 mL/min and were composed of (A) 5% acetonitrile in phosphate buffer, pH 3 and (B) acetonitrile. The gradient profile was 20% B (0 min), 20% (0.5 min), 30% B (3 min) and 20% B (4 min). The analytes were detected by UV in the spectrum from 200 nm to 400 nm. The lower limit of the assay was 0.1 mg/L in plasma (coefficients of variation %=18.2%).

Results are presented as medians with IQR and range. Statistical differences between mothers and infants were tested with the Wilcoxon signed-rank test for non-normal data. Two-sided p values less than 0.05 were accepted as statistically significant. The data analyses were performed by the statistical software available in GraphPad Prism V.8 (GraphPad, La Jolla, California, USA).

Written consent was obtained from all women, and from one or both parents on behalf of the infant. This project was approved by the Danish Scientific Ethics Committee as an amendment to the original protocol.

RESULTS

Characteristics of 76 mothers and their infants are presented in table 1. Indications for IAP were one of the following risk factors (1) a GBS culture positive urine (≥10×4 CFU/mL) during current pregnancy, (2) prolonged rupture of membranes or (3) 35 or 36 weeks gestation at birth, and a positive intrapartum GBS PCR for 43 women (56.6%) and 'other' for 44 women (57.9%). 'Other' included preterm labour, previous child with confirmed or suspected EOGBS, breakdown of POCT intrapartum PCR equipment or borderline results along with one or more risk factors. Some women fulfilled more than one criterion. The characteristics of the women were similar to those of the entire cohort of 1042 women.[17] The median Body Mass Index was 23.8 (IQR 21.5–27.4 kg/m^2). 37 (48.7%) mothers received only one dose of IAP, 19 (25 %) received two doses and 20 (26.3%) received three or more doses.

Since infant and maternal samples were only available for 44 mother–infant dyads, results on penicillin G concentrations are reported on the 44 mother–infant dyads. Median maternal penicillin G concentration was 0.2 mg/L (IQR 0–0.8 mg/L; range 0–1.6 mg/L).

Median infant penicillin G concentration was 1.2 mg/L (IQR 0.5–5.0 mg/L; range 0–12.7 mg/L). Three infants had a concentration below the lower limit of quantification of 0.1 mg/L. These were born between 1.5 and 3.5 hours after maternal penicillin G administration. The most likely explanation for this is an erroneous swap of infant and maternal samples.

Penicillin G plasma concentrations in relation to the time interval between administration and delivery (mothers) and birth (umbilical cord, infants) are shown in table 2. The highest concentrations were found in infants who were born within 1 hour of IAP administration; median: 5.54 mg/L (IQR 3.42–8.27 mg/L) (n=7), and lowest in infants born 3–4 hours after IAP; median: 0.46 mg/L (IQR 0.19–1.01 mg/L) (n=6). Infant penicillin G concentrations far exceeded the MIC (0.125 mg/L) even for short time intervals between maternal administration and delivery.

Table 1 Characteristics of mothers (N=76) and their infants (N=76) at birth

Parameters	Penicillin G
Mothers	
N	76
Age (years)*	29 (27–32)
BMI (kg/m^2)*	23.8 (21.5–27.4)
Smoking†	3 (3.9)
Thyroid disease†	2 (2.6)
Diabetes type I†	1 (1.3)
Diabetes type II†	0 (0.0)
Hypertension†	1 (1.3)
Pregnancy complications	
Gestational diabetes†	2 (2.6)
Gestational hypertension†	7 (9.2)
Pre-eclampsia†	4 (5.3)
Indication for antibiotic treatment	
Intrapartum GBS PCR positive†	43 (56.6)
Other†‡	44 (57.9)
Doses of penicillin G	
1 dose	37 (48.7)
2 doses	19 (25.0)
≥3 doses	20 (26.3)
Infants	
N	76
Gestational age (week, day)*	39.3 (38.1–40.5)
Preterm birth (<37 weeks)†	5 (6.6)
Birth weight (g)*	3498 (3137–3908)
Admission to neonatal intensive care unit (days) (n=16)*	Median 5 (1–98)

*Results are presented as median (IQR)
†Results are presented as n (%)
‡'Other' refers to preterm labour, previous child with EOGBS or other neonatal infection, GBS in urine during pregnancy, breakdown of POCT intrapartum PCR equipment or borderline results.
BMI, Body Mass Index; EOGBS, early-onset group B streptococcus disease; GBS, group B streptococcus.

Table 2 Penicillin G plasma concentrations in relation to the time interval between administration and delivery (mothers) and birth (cord blood infants)*†

Mothers	
Time interval from administration of antibiotics to delivery	Penicillin G (mg/L) N=44
<1 hour	0.17 (0.00–0.53) (n=7)
1–2 hours	0.93 (0.00–1.07) (n=11)
2–3 hours	0.00 (0.00–0.68) (n=14)
3–4 hours	0.17 (0.00–0.71) (n=6)
>4 hours	0.00 (0.00–0.49) (n=6)
Infants	
Time interval from administration of antibiotics to birth	Penicillin G (mg/L) N=44
<1 hour	5.54 (3.42–8.27) (n=7)
1–2 hours	2.97 (0.67–5.16) (n=11)
2–3 hours	1.28 (0.68–3.28) (n=14)
3–4 hours	0.46 (0.19–1.01) (n=6)
>4 hours	0.66 (0.44–1.43) (n=6)

*Results are presented as median (IQR).
†The recommended interval of 4 hours between two doses of penicillin G was not always followed. Of the 38 infants who were born 4 hours or less after the first dose, 18 received one dose, 11 received two doses and 9 received three or more doses.

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Figure 1 illustrates how the highest plasma concentrations were reached in umbilical cord blood within 1 hour between the administration and birth; the umbilical cord concentrations increase during the first 60 min after the administration as the penicillin G crosses the placenta, makes its way into the fetal circulation and then decreases over the next hours by combined efforts of maternal and fetal clearance.

The relationship between antibiotic plasma penicillin G concentrations in mother–infant dyads (N=44), with very low maternal concentrations compared with their infants' is illustrated in figure 2A,B. Particularly, very high concentrations are seen in the infants of the 20 dyads who only received one dose of IAP. Median infant concentration for these 20 infants was 5.0 mg/L (IQR 1.5–7.4 mg/L; range 0–12.7 mg/L). For the 24 infants exposed to more than one dose, median penicillin G concentration was 0.8 mg/L (IQR 0.5–1.3 mg/L; range 0–5.3 mg/L). The median time from last given penicillin G dose to delivery was 36 min (IQR 76–193 min).

16 infants of the 76 mothers who received penicillin G were admitted to neonatal intensive care unit with a median hospital stay of 5 days (1–98 days); none with EOGBS.

With a median of 1.2 mg/L, the majority of infant penicillin G concentrations far exceeded the MIC (0.125 mg/L) even for short time intervals between maternal administration and delivery.

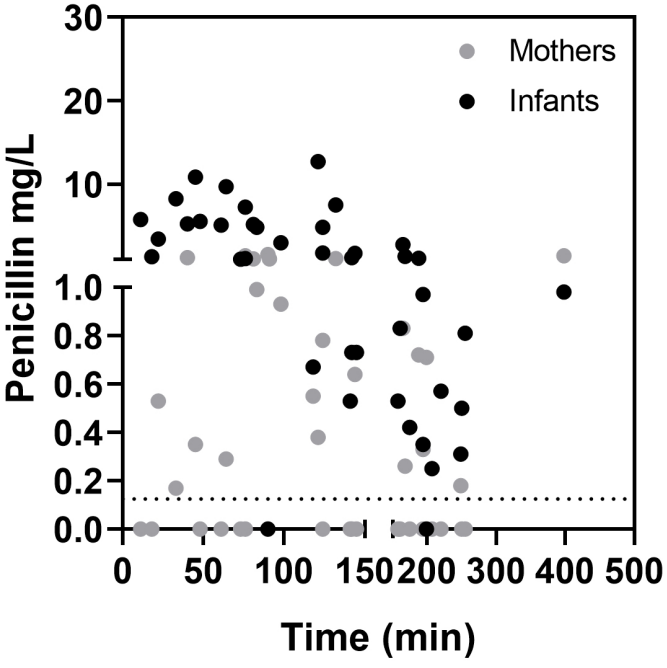

Figure 1 Plasma concentrations of antibiotics in 44 mothers and infants plotted against time from administration of the antibiotic to delivery (time of sampling from umbilical cord). Mothers: grey dots. Infants: black dots. Dotted line: Penicillin minimal inhibitory concentration for group B streptococcus: 0.125 mg/L.

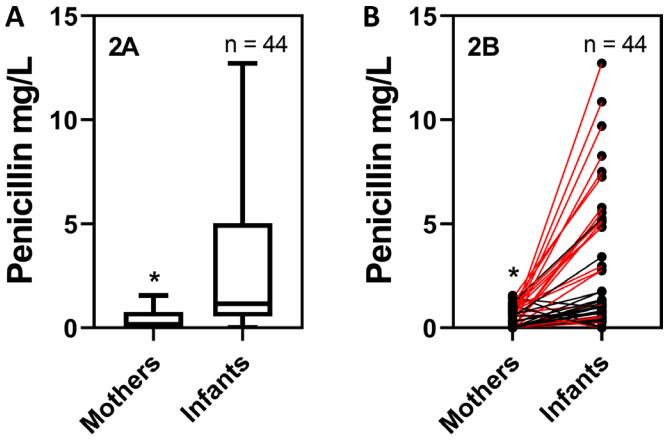

Figure 2 Plasma concentrations of antibiotics in 44 mother–infant dyads. Significant differences between mother and infant were estimated with the Wilcoxon's signed-rank test with a significant level of p<0.05. Significant differences are shown with asterisks. (A) Data are shown as a box plot showing medians, IQR and range (min–max). (B) The individual pairs are shown with lines and symbols. Red lines (N=20): mother–infant dyads who only received one dose of intrapartum antibiotic prophylaxis.

DISCUSSION

We report high concentrations of penicillin G in umbilical cord blood of infants born less than 4 hours after the last IAP administration of their mothers. Our study demonstrates how short intrapartum exposure to penicillin G leads to significantly higher levels in the infant's bloodstream than in the mothers, well above the MIC for GBS.

Our findings are in line with those of Barber *et al*[11] who studied umbilical cord samples but had no maternal samples for comparison. With slightly higher umbilical cord concentrations than in our study, they found that fetuses exposed to IAP less than 1 hour prior to birth had substantially higher penicillin G levels compared with those exposed to over 2 hours before birth. Berardi *et al*[14] assessed ampicillin levels in cord blood and found that ampicillin levels reached a peak in umbilical cord blood within 30 min after IAP administration.

Guidelines for infants exposed to less than 4 hours of IAP

Scasso *et al*[18] used GBS positive rectovaginal swabs taken during labour before IAP and 2 and 4 hours after IAP administration to conclude that 4 hours of IAP was needed for the purposes of neonatal management. Other previous studies evaluated the efficacy of intrapartum beta-lactam given less than 4 hours before birth by examining skin or pharynx GBS colonisation of the infants.[19] However, these are only surrogate markers for invasive GBS infection.

Center for Disease Control and Prevention's (CDC) GBS prevention guideline[9] considers asymptomatic infants at risk if born to mothers colonised with GBS and received less than 4 hours of IAP based on previous studies.[20] However, investigations of the reasons behind the infants receiving <4 hours of IAP are lacking.

The CDC's GBS prevention guideline from 2002[8] recommended that infants with <4 hours of IAP exposure should be evaluated with a blood culture and complete blood count immediately after birth. However, in the revised version from 2010,[9] well-appearing infants with less than 4 hours of IAP exposure can be managed by in-hospital observation for at least 48 hours after birth. For infants with known risk factors of EOGBS, limited evaluation and observation for at least 48 hours are still recommended. National guidelines now incorporate the increasing use of intrapartum GBS PCR testing and in 2019, the American Academy of Pediatrics outlined three approaches to risk assessment for infants born at or after 35 weeks which all imply 36–48 hours of observation.[10]

In infants, several preconditions may influence measures of antibiotic concentrations. These include gestational age, weight and body surface area. Immature renal clearance that can increase the half-life of the given antibiotic and the rate of placental transfer may be reasons for the high concentrations found among infants exposed to only one dose of IAP along with the fact that the first maternal dose is 3 g whereas the following doses are 1.5 g. Based on the studies by Barber *et al* [11] and Berardi *et al 14* , a review by Berardi *et al 21* concludes that there is no reason to suppose a lower effect of short IAP duration when the entire loading dose has been administered.

EOGBS in infants with less than 4 hours of IAP, 4 hours or more IAP and debut of symptoms

Given that many women with risk factors do not receive the recommended 4 hours or more IAP,[22 23] it seems relevant to study the distribution of EOGBS in relation to the duration of IAP. Nanduri *et al*[24] evaluated duration of antibiotic exposure in 322 cases of EOGBS and found that 196 mothers (61%) received IAP less than 4 hours whereas 126 mothers (39%) received IAP 4 hours or more before delivery. The time of infant onset of symptoms was not provided.

Berardi *et al* evaluated symptoms in 191 infants with invasive GBS. A total of 48 were exposed to IAP, 32 (67%) had symptoms at birth; of these, 17 were exposed to less than 4 hours of IAP and 7 to more than 4 hours of IAP (2 received unknown duration; 6 received non-beta-lactams).[25] The authors concluded that most infants with invasive GBS disease exposed to IAP had symptoms at birth regardless of IAP duration and that infants exposed to a relevant antimicrobial agent who remain asymptomatic in the first 6 hours of life are likely uninfected.

Berardi *et al* also reported how almost all term infants with confirmed EOGBS exposed to IAP had symptoms at birth, regardless of duration of exposure and number of IAP doses The unexposed neonates in their cohort, on the other hand, developed EOGBS hours after birth.[21]

When IAP fails to seem to protect the infants, it raises the question of reverse causality; if the fetus was already infected at the time of administration and the short IAP was due to rapid delivery caused by fetal distress. In this scenario, the transfer of antibiotics could perhaps also be compromised due to placental infection.

A strength of our study is the availability of time of IAP administration and time of delivery. An obvious limitation is the few blood samples from mother–infant dyads with registration of time and doses of penicillin G administration.

The antibacterial activity of beta-lactam antibiotics is related to the time above the MIC (T>MIC) of the free, unbound drug concentration and maximising T>MIC increases the therapeutic impact.[14] Therefore, using one concentration relative to MIC as in our study, is not ideal, but indicative of the potential therapeutic impact.

Our study indicates that it may be inaccurate to consider all infants exposed to only one dose of IAP for less than 4 hours at risk for EOGBS. Therefore, future studies need to evaluate if well-appearing infants could be discharged sooner than the currently recommended 36–48 hours of in-hospital observation. In order to change clinical practice, pharmacokinetic studies with infant follow-up samples after birth are warranted to gain

insight into the distribution and metabolism of the penicillin G that the infant has received as a fetus.

CONCLUSION

In summary, our study shows penicillin G levels well beyond MIC in infants born within 4 hours of maternal IAP with very high concentrations in infants with only one dose of IAP. Our findings challenge the assumption that all infants exposed to IAP for less than 4 hours are less protected than those with IAP at 4 hours or two or more IAP doses.

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Contributors SYN concepted and designed the study, collected and interpreted data. EH-L concepted and designed the study, performed the HPLC analysis, interpreted data. TBH concepted and designed the study, interpreted data. CMH collected and interpreted data. RBH included patients, interpreted data. MRK included patients, interpreted data. JKM concepted and designed the study, interpreted data. LHP concepted and designed the study, interpreted data. MM collected and interpreted data. EG concepted and designed the study, performed the HPLC analysis, performed the statistical analysis, interpreted data. SYN is guarantor of the overall content.

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