

JPPT | Single-Center Retrospective Study

# Neonatal Serum Gentamicin Concentrations and Outcomes Following Maternal Once-Daily Gentamicin Dosing

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**OBJECTIVE** This study evaluated newborn gentamicin serum concentrations after birth and the effects on the newborn after extended interval gentamicin dosing in peripartum mothers.

**METHODS** This was a single-center, retrospective chart review of neonates born to mothers that received peripartum once-daily gentamicin dosing of approximately 5 mg/kg within 12 hours of delivery. A gentamicin serum concentration was obtained immediately after birth in the newborn. The primary outcome was initial neonatal gentamicin serum concentration after birth. Several secondary outcomes were evaluated including nephrotoxicity and ototoxicity. A subgroup analysis comparing baseline demographics of mother-newborn dyads with birth neonatal serum concentrations of less than 2 mcg/mL versus 2 mcg/mL or greater was performed.

**RESULTS** A total of 32 mother-newborn dyads were included. Newborns had a median gestational age of 39.4 weeks and median birth weight of 3.4 kg. The mean initial gentamicin serum concentration was elevated at  $3.1 \pm 1.9$  mcg/mL among all newborns. The median maternal dose based on actual body weight in newborns with gentamicin serum concentrations less than 2 mcg/mL was 3.5 (IQR, 3.3–4.8) mg/kg versus 4.8 (IQR, 4.3–5.2) mg/kg in those that had serum concentrations of 2 mcg/mL or greater ( $p = 0.025$ ). All newborn gentamicin serum concentrations were less than 2 mcg/mL for maternal doses given less than 1 hour prior to delivery ( $n = 8$ ). There were no significant differences in nephrotoxicity or ototoxicity.

**CONCLUSIONS** Peripartum once daily dosing of gentamicin administered between 1 to 12 hours of birth may lead to clinically significant serum concentrations in newborns.

**ABBREVIATIONS** MIC, minimum inhibitory concentration; NSAID, nonsteroidal anti-inflammatory drug; ODD, once-daily dose; TIDD, three times daily dosing

**KEYWORDS** gentamicin; neonate; once-daily dosing; peripartum; serum concentrations

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## Introduction

Gentamicin is a broad-spectrum antibiotic commonly used in peripartum women for various obstetric-gynecologic infections, including chorioamnionitis.<sup>1–4</sup> Gentamicin can be dosed as conventional 3 times daily dosing (TIDD) or a larger once-daily dose (ODD) depending on patient-specific factors.<sup>1–4</sup> Historically, gentamicin has been more commonly dosed using conventional TIDD for pregnant mothers. As we have learned more about the pharmacokinetic and pharmacodynamic properties of aminoglycosides, we know that ODD helps to optimize efficacy and minimize toxicity.<sup>1</sup> This is achieved through higher peak to minimum inhibitory concentration (MIC) ratios resulting in optimal bacterial killing and a more sustained post-antibiotic effect. Additionally, ODD minimizes adverse effects, such as nephrotoxic-

ity and ototoxicity, by allowing for longer medication free periods leading to less drug accumulation. Given literature to support the efficacy of ODD of 5 mg/kg in pregnant mothers for chorioamnionitis, our institution adjusted its maternal gentamicin dosing from TIDD to ODD in peripartum women in October 2019. Mothers received a gentamicin dose of approximately 5 mg/kg (rounded to the nearest predetermined flat dose based on actual body weight) up to a maximum of gentamicin 480 mg per institutional guideline.

Gentamicin doses readily cross the placenta and have been shown to accumulate in fetal cord blood.<sup>5–7</sup> Studies have identified detectable but not clinically significant gentamicin serum concentrations in newborns born to mothers receiving conventional TIDD gentamicin prior to delivery.<sup>2,5–9</sup> It would be expected that ODD

of gentamicin 5 mg/kg given peripartum to the mother would result in higher gentamicin serum concentrations in the newborn following delivery.<sup>2,5-9</sup> Locksmith et al<sup>2</sup> found that extrapolated peak cord serum concentrations based off of cord blood concentrations obtained at delivery were 6.9 mcg/mL in the maternal ODD gentamicin neonates compared with 2.9 mcg/mL in the conventional dosing group. A peak gentamicin serum concentration of 6 to 8 mcg/mL would be considered clinically therapeutic for the treatment of neonatal sepsis.<sup>2</sup> A theoretical safety concern for the neonate born to a mother receiving ODD gentamicin is that serum concentrations would still be elevated upon first-dosing in the neonate, thus leading to supratherapeutic peak concentrations after the initial dose and a prolonged period of gentamicin serum concentrations above 2 mcg/mL. This could increase the risk of gentamicin ototoxicity and nephrotoxicity in the neonate.

Due to the change in gentamicin dosing for chorioamnionitis to ODD in peripartum mothers at our institution, there was a concern for clinically significant gentamicin serum concentrations in the newborn. Our institution elected to obtain a STAT random gentamicin serum concentration after birth when maternal gentamicin was administered within the 12 hours of delivery and initiation of gentamicin therapy was warranted in the newborn. Specific institutional dosing recommendations based on this gentamicin serum concentration were developed taking into account population-based pharmacokinetics for newborns and assuming that a therapeutic peak concentration was achieved in utero upon maternal dosing (Table 1).

The goal of this analysis was to evaluate initial birth gentamicin serum concentrations and the effects on the newborn after ODD of gentamicin in peripartum mothers, including an evaluation of safety of our institutional guideline.

## Materials and Methods

This was a single-center, non-randomized, retrospective chart review of all neonates requiring initiation of gentamicin at birth who were born to mothers that received peripartum ODD of gentamicin within 12 hours of delivery. The timeframe of 12 hours was chosen based on elimination half-life kinetics in peripartum patients of

1.4 to 1.8 hours and data showing serum concentrations < 2 mcg/mL approximately 12 hours after ODD.<sup>2,3</sup> Neonatal patients born at The University of Chicago Medicine and admitted to the neonatal intensive care unit between October 2019 and March 2020 who had a STAT random gentamicin serum concentration obtained immediately after birth per the institutional guideline were included. Subjects were excluded from the analysis if maternal gentamicin prior to delivery was not ODD. No neonates were excluded based on renal dysfunction as this would not have been evident immediately after birth. The primary outcome was initial neonatal gentamicin serum concentration at birth. Secondary outcomes included compliance with our institutional guideline, nephrotoxicity (defined as an increase in serum creatinine by 0.3 mg/dL or 1.5× baseline or greater in the first 7 days of life, a urine output less than 0.5 mL/kg/hr in the first 24 hours of life, or a urine output less than 1 mL/kg/hr between 24 to 72 hours of life), ototoxicity (defined as a final failed hearing screen prior to discharge), positive cultures, time to clearance of blood culture, and mortality. The serum creatinine and urine output values for acute kidney injury were selected based on the 2012 Kidney Disease: Improving Global Outcomes Clinical Practice Guideline for Acute Kidney Injury with the exception of a lower cutoff for urine output in the first 24 hours of life, which was chosen since newborns typically have a delay in producing urine after birth.<sup>10</sup> The timeframe for urine output cutoff at 72 hours of life compared with a serum creatinine elevation 7 days after birth was chosen to take into account that changes in urine output in the setting of acute kidney injury generally occur faster than changes in serum creatinine. Compliance to the guideline was assessed based on appropriate attainment of initial gentamicin serum concentration before dose verification in the neonate and appropriate dosing and timing of administration of gentamicin (within 1 hour) following the neonate's gentamicin serum concentration based on our institutional guideline. A subgroup analysis comparing 2 groups based on initial birth gentamicin serum concentrations of less than 2 mcg/mL (Appropriate Level Group) versus 2 mcg/mL or greater (Supratherapeutic Level Group) was performed.

Data collection included maternal information regarding actual and ideal body weight, gentamicin

**Table 1.** Institutional Neonatal Gentamicin Dosing Algorithm

Gentamicin Serum Concentration, mcg/mL	Birth Weight < 2 kg	Birth Weight ≥ 2 kg
≥ 6	36 hr after level, start gentamicin 4 mg/kg q36h	24 hr after level, start gentamicin 4 mg/kg q24h
4 to < 6	24 hr after level, start gentamicin 4 mg/kg q36h	12 hr after level, start gentamicin 4 mg/kg q24h
2 to < 4	12 hr after level, start gentamicin 4 mg/kg q36h	6 hr after level, start gentamicin 4 mg/kg q24h
< 2	Now, start gentamicin 4 mg/kg q36h	Now, start gentamicin 4 mg/kg q24h

dose, administration time, gentamicin indication, and pertinent culture results. Neonatal information collected included initial gentamicin serum concentration, timing of first dose of gentamicin, gentamicin dose (milligrams) administered, gentamicin dose frequency, potential nephrotoxins or agents influencing renal perfusion (acyclovir, amphotericin B, loop diuretics, nonsteroidal anti-inflammatory drugs [NSAIDs], vasopressors, and vancomycin) or ototoxins (loop diuretics and NSAIDs) received, urine output, serum creatinine, positive blood culture results, treatment duration, and mortality.

Data are presented as percentages for nominal variables and as median (IQR) or mean  $\pm$  SD as appropriate for continuous variables. Statistical analyses were performed with STATA software (Stata Statistical Software Release 14; StataCorp LP, College Station, TX). Comparisons between subgroups were analyzed using the Fisher exact test or Pearson  $\chi^2$  test for categorical data, as appropriate. For continuous data, groups were compared using the Mann-Whitney rank sum test or Student *t* test, as appropriate. A linear regression analysis was performed to evaluate the correlation between various baseline demographics and newborn gentamicin serum concentrations. A *p* value  $<$  0.05 was considered statistically significant.

## Results

Thirty-two mother-newborn dyads were included in this evaluation. Baseline demographics are shown in Table 2. Mean maternal age was  $29.2 \pm 5.6$  years, median actual body weight was 79 kg (IQR, 69.5–90), and mean ideal body weight was  $53.3 \pm 5.9$  kg. The median time from gentamicin administration to delivery was 1.8 hours (IQR, 0.8–3.3).

Newborns had a median gestational age of 39.4 weeks (IQR, 37.4–40.2) and median birth weight of 3.4 kg (IQR, 3–3.7). The median time between delivery and measured neonatal serum gentamicin concentration was 43 minutes (IQR, 37–64.5). Few neonates received concomitant ototoxic (*n* = 2) or nephrotoxic medications (*n* = 1).

Median maternal actual body weight was similar between the groups with 82.6 kg (IQR, 67.1–136.3) in the Appropriate Level Group and 78 kg (IQR, 70.7–84.8) in the Supratherapeutic Level Group (*p* = 0.592) as shown in Table 2. However, there was a significant difference in mean maternal ideal body weight at  $56.8 \pm 4.9$  kg versus  $51.5 \pm 5.7$  kg, respectively (*p* = 0.014). There was also a significant difference in maternal dose in mg/kg based on both ideal body weight (*p* = 0.009) and actual body weight (*p* = 0.025). The time between maternal gentamicin administration and time of delivery varied between

**Table 2.** Baseline Mother-Newborn Dyad Demographics

Characteristic	All Subjects (N = 32)	Appropriate Level Group	Supratherapeutic Level Group	p value
		Gentamicin < 2 (n = 11)	Gentamicin $\geq$ 2 (n = 21)	
<b>Maternal</b>				
Age, mean $\pm$ SD, yr	29.2 $\pm$ 5.6	30.7 $\pm$ 5.4	28.4 $\pm$ 5.7	0.271
Actual body weight, median (IQR), kg	79 (69.5–90.0)	82.6 (67.1–136.3)	78.0 (70.7–84.8)	0.592
Ideal body weight, mean $\pm$ SD, kg	53.3 $\pm$ 5.9	56.8 $\pm$ 4.9	51.5 $\pm$ 5.7	0.014
Height, mean $\pm$ SD, inches	63.4 $\pm$ 2.6	64.9 $\pm$ 2.1	62.6 $\pm$ 2.5	0.010
Serum creatinine, mean $\pm$ SD, mg/dL	0.8 $\pm$ 0.3	0.6 $\pm$ 0.1	1 $\pm$ 0.3	0.047
Gentamicin dose for maternal ideal body weight, mean $\pm$ SD, mg/kg	6.8 $\pm$ 1.7	5.8 $\pm$ 2.0	7.4 $\pm$ 1.3	0.009
Gentamicin dose for maternal actual body weight, median (IQR), mg/kg	4.6 (4.0–5.1)	3.5 (3.3–4.8)	4.8 (4.3–5.2)	0.025
Positive cultures, n (%)	0 (0)	0 (0)	0 (0)	1.000
Time between gentamicin administration and delivery, median (IQR), hr	1.8 (0.8–3.3)	0.5 (0.3–1.4)	2.6 (1.7–3.4)	0.005
<b>Neonatal</b>				
Gestational age, median (IQR), wk	39.4 (37.4–40.2)	39.1 (35.0–40.3)	39.4 (38.6–40.1)	0.842
Weight, median (IQR), kg	3.4 (3.0–3.7)	3.7 (2.9–3.9)	3.4 (3.0–3.7)	0.525
Male sex, n (%)	20 (62.5)	7 (63.6)	13 (61.9)	1.000
Time between delivery and serum gentamicin concentration, median (IQR), min	43 (37–64.5)	43 (36–80)	43 (37–64)	0.781
Other ototoxic medications during admission, n (%)	2 (6.3)	1 (9.1)	1 (4.8)	1.000
Other nephrotoxic medications during admission, n (%)*	1 (3.1)	1 (9.1)	0 (0)	0.344

\* Includes agents with the potential to influence renal perfusion.

the groups with a median time of 0.5 hours (IQR, 0.3–1.4) in the Appropriate Level Group versus 2.6 hours (IQR, 1.7–3.4) in the Supratherapeutic Level Group ( $p = 0.005$ ).

The mean initial newborn gentamicin serum concentration was elevated at  $3.1 \pm 1.9$  mcg/mL among all newborns (Table 3). The mean gentamicin serum concentration was  $0.9 \pm 0.6$  mcg/mL in the Appropriate Level Group compared with  $4.2 \pm 1.3$  in the Supratherapeutic Level Group ( $p < 0.0001$ ). One patient in the Supratherapeutic Level Group had hearing failure with a failed in-hospital screening prior to discharge while no neonates in the Appropriate Level Group had ototoxicity. Five neonates had nephrotoxicity, with 2 in the Appropriate Level Group and 3 in the Supratherapeutic Level Group. Most of these neonates ( $n = 31$ ) did not receive concomitant nephrotoxic medications. One neonate in the Appropriate Level Group did receive an NSAID during the same time period. There was no mortality in either group within 14 days of gentamicin therapy. One newborn had a positive blood culture

after birth. It speciated to *Escherichia coli* and cleared within 24 hours.

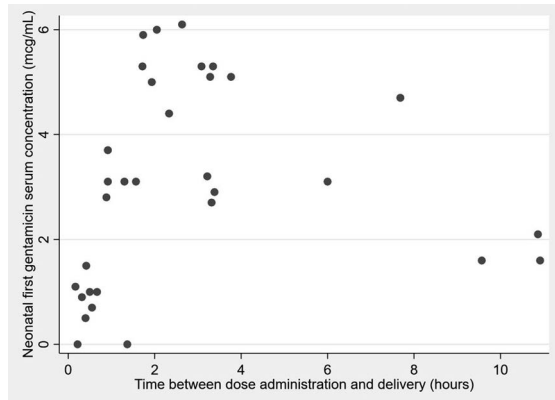
All newborn gentamicin serum concentrations were less than 2 mcg/mL for maternal doses given less than 1 hour prior to delivery ( $n = 8$ ; Figure 1). There was no correlation between maternal actual body weight and neonatal gentamicin serum concentrations ( $R^2 = 0.0124$ ; Figure 2A), while there was a very weak correlation with maternal ideal body weight ( $R^2 = 0.1772$ ; Figure 2B). There was a very weak correlation between maternal serum creatinine and neonatal gentamicin serum concentrations ( $R^2 = 0.1944$ ; Figure 3). There was also a very weak correlation between maternal gentamicin dose (milligrams per kilogram based on actual body weight) and neonatal gentamicin serum concentration ( $R^2 = 0.1680$ ; Figure 4A), as well as between maternal gentamicin dose (milligrams per kilogram based on ideal body weight) and neonatal gentamicin serum concentrations ( $R^2 = 0.2405$ ; Figure 4B).

**Table 3.** Neonatal Clinical Outcomes

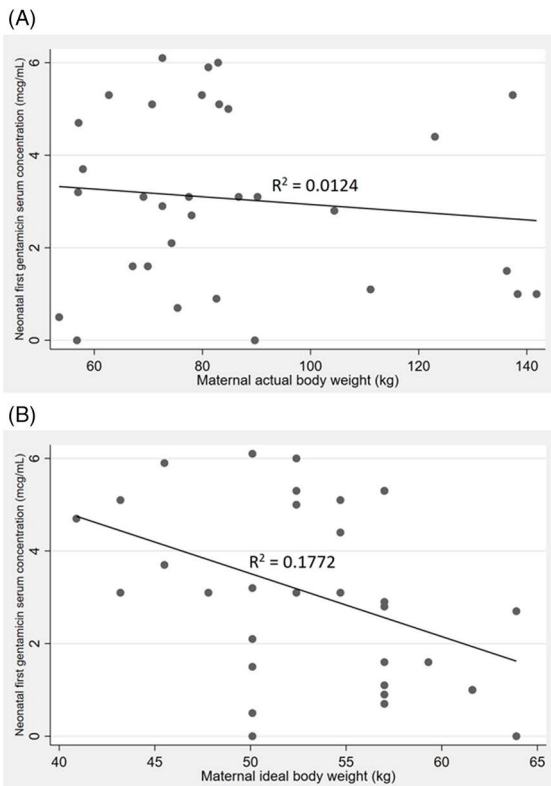
Outcomes	All Subjects (N = 32)	Appropriate Level Group	Supratherapeutic Level Group	p value
		Gentamicin < 2 (n = 11)	Gentamicin ≥ 2 (n = 21)	
Initial serum gentamicin concentration, mean ± SD, mcg/mL	3.1 ± 1.9	0.9 ± 0.6	4.2 ± 1.3	< 0.0001
Gentamicin duration for initial course, median (IQR), days	2 (2–3)	3 (2–3)	2 (2–2)	0.069
Compliance with protocol, n (%), yes	26 (81.3)	9 (81.8)	17 (81.0)	1.000
Failed initial hearing screen, n (%)	2 (6.3)	1 (9.1)	1 (4.8)	1.000
Failed repeat hearing screen, n (%)	1 (3.1)	0 (0)	1 (4.8)	1.000
Initial serum creatinine, median (IQR), mg/dL	0.8 (0.7–0.9)	0.8 (0.6–0.9)	0.8 (0.7–0.9)	0.688
Maximum serum creatinine in the first 7 DOL, median (IQR), mg/dL	0.9 (0.7–0.9)	0.85 (0.6–0.9)	0.9 (0.7–0.9)	0.756
Nephrotoxicity, n (%)	5 (15.6)	2 (18.2)	3 (14.3)	1.000
Serum creatinine increase by 0.3 mg/dL or 1.5× baseline or greater in the first 7 DOL, n (%)	2 (6.3)	1 (9.1)	1 (4.8)	1.000
UOP < 0.5 mL/kg/hr for HOL 0–24, n (%)	1 (3.1)	0 (0)	1 (4.8)	1.000
UOP < 1 mL/kg/hr for HOL 24–48, n (%)	1 (3.1)	0 (0)	1 (4.8)	1.000
UOP < 1 mL/kg/hr for HOL 48–72, n (%)	1 (3.1)	1 (9.1)	0 (0)	0.344
Positive blood culture within the first 72 HOL, n (%)	1 (3.1)	0 (0)	1 (4.8)	1.000
Organism			<i>E coli</i> (S to gentamicin)	
Days to clearance of culture			1	
14-day mortality, n (%)	0 (0)	0 (0)	0 (0)	1.000

DOL, days of life; HOL, hours of life; S, susceptible; UOP, urine output

**Figure 1.** Comparison of maternal gentamicin time from administration to delivery and neonatal serum gentamicin concentrations.

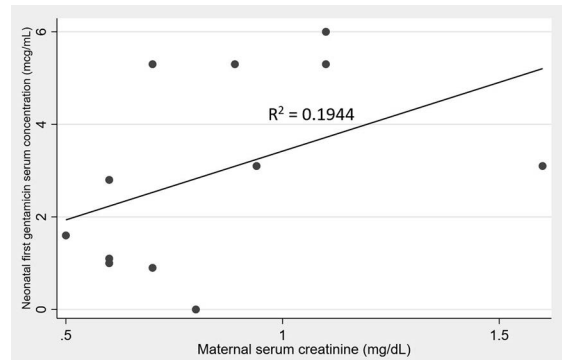


**Figure 2.** Comparison of maternal weight and neonatal gentamicin serum concentrations: (A) based on maternal actual body weight; (B) based on maternal ideal body weight.

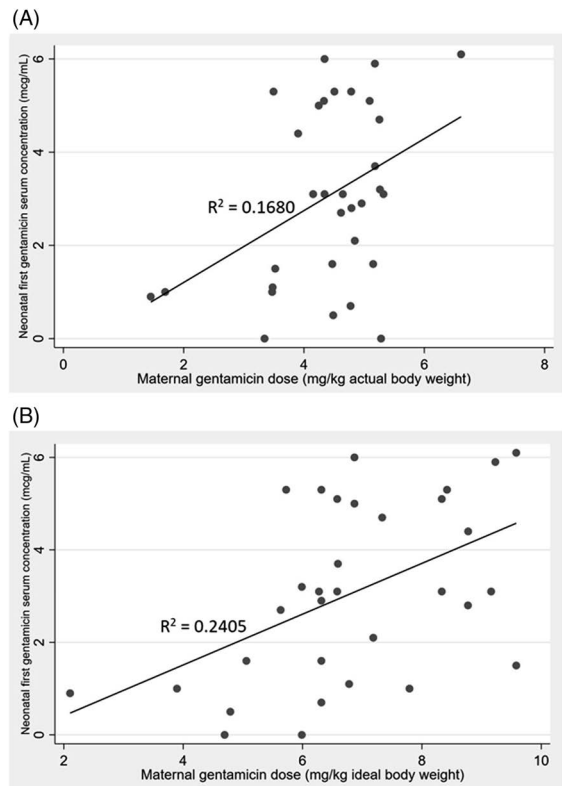


The medical team was compliant with the guideline for 81.3% (26 of 32) of patients. For the 6 patients in whom the guideline was not followed, 4 had doses initiated too late and 2 had doses initiated too soon. These variations from the guideline were not associated with negative outcomes.

**Figure 3.** Comparison of maternal serum creatinine and neonatal gentamicin serum concentration.



**Figure 4.** Comparison of maternal gentamicin dose and neonatal gentamicin serum concentration: (A) based on maternal actual body weight; (B) based on maternal ideal body weight.



### Discussion

It would be expected that gentamicin ODD of 5 mg/kg given peripartum to the mother would result in higher gentamicin serum concentrations in the newborn following delivery than TIDD with lower individual doses. Our evaluation supports this, with an average initial gentamicin concentration in the newborn after

birth of  $3.1 \pm 1.9$  mcg/mL. This analysis further evaluated outcomes associated with these initial serum concentrations. Gentamicin administered less than 1 hour prior to delivery resulted in birth gentamicin serum concentrations less than 2 mcg/mL for all 8 neonates evaluated. This may be due to the fact that administration was so near delivery that there was inadequate time for meaningful distribution of gentamicin to the fetus prior to delivery. Additionally, there were 3 values (Figure 1) assessed in newborns with mothers receiving gentamicin 8 to 12 hours prior to delivery that were near 2 mcg/mL or less, indicating a need for further investigation in this specific timeframe to determine when maternal ODD gentamicin doses are likely to clear to a safe concentration in the newborn.

As mentioned previously, there were 6 deviations from the guideline. For the 4 patients with late administration of gentamicin, no serum concentrations were greater than 4 and no subsequent serum concentrations were obtained. All of these late administrations occurred during overnight hours when staffing is limited, which may be a contributing factor. These deviations from protocol were not associated with negative outcomes. Education was given to any personnel not following protocol to reinforce the changes that had been implemented.

Regarding safety outcomes, there was no difference noted in the incidence of nephrotoxicity or ototoxicity in patients with an initial gentamicin serum concentration of 2 mcg/mL or greater or less than 2 mcg/mL. Long-term follow up of the newborn that failed their inpatient hearing screening was unable to be determined. These data, while limited in sample size, support the hypothesis that ODD gentamicin peripartum is likely safe in newborns and that elevated gentamicin serum concentrations at birth do not increase the risk of ototoxicity or nephrotoxicity when adjustments based on population pharmacokinetic parameters are made. Further studies are needed to validate these findings.

One patient in the Supratherapeutic Level Group had a positive blood culture after birth that grew *E coli*, which was ampicillin resistant and gentamicin susceptible. The maternal dose was 4.6 mg/kg based on actual body weight and was administered 3.3 hours prior to delivery. The neonate's initial gentamicin concentration was elevated at 2.7 mcg/mL. Our institutional guideline was followed appropriately, and the first gentamicin dose to the newborn was delayed by 12 hours to allow for clearance of maternal gentamicin. The infant was hemodynamically stable and received a full antibiotic course for treatment, switching from gentamicin after 3 days to cefotaxime due to a preference to treat with beta-lactams for Gram-negative bacteremia. Only the initial blood culture was positive, and all future blood cultures were negative. Serum gentamicin concentrations were used to perform the pharmacokinetic analysis to obtain the desired data. The pharmacokinetic variables

calculated at steady state were as follows: peak of 8.5 mcg/mL, trough of 0.76 mcg/mL, half-life of 10.2 hours, elimination constant of  $0.068 \text{ hour}^{-1}$  and a volume of distribution of 0.5 L/kg. The neonate failed a repeat hearing screening in both ears and did not receive any additional potentially nephrotoxic or ototoxic medications prior to hearing screening. While not definitive since this is only 1 case, it may alleviate the concern that intentionally delaying the first dose of gentamicin to the newborn based on initial serum gentamicin concentration may reduce the likelihood of effectively treating early-onset Gram-negative bacteremia. It also further creates interest in whether higher maternal ODD may actually result in arguably earlier treatment of the newborn while still *in utero*, since therapeutic gentamicin serum concentrations can be obtained in the fetus prior to delivery with this dosing strategy.<sup>2</sup>

There was a very weak correlation for 3 maternal baseline demographics (maternal ideal body weight, maternal serum creatinine, and maternal milligrams-per-kilogram gentamicin dose based on actual body weight) when compared with neonatal serum gentamicin concentrations (Figures 3 and 4, respectively). These baseline demographics relative to maternal ODD gentamicin and its effects on the newborn warrant further research.

This study had limitations including a small sample size and being conducted at a single center. There was a lack of outpatient auditory clinic follow up, which limits the evaluation of ototoxicity as hearing loss can occur several weeks after aminoglycoside therapy has been discontinued. Additionally, the current institutional guideline only obtains 1 initial gentamicin serum concentration so subsequent therapeutic drug monitoring to assess pharmacokinetic parameters was not completed on every patient.

## Conclusion

In summary, this study suggests peripartum ODD of gentamicin may lead to clinically significant serum concentrations in newborns if administered between 1 to 12 hours prior to delivery. No clinically apparent concerns for nephrotoxicity or ototoxicity were seen. Institutions should consider development of therapeutic drug monitoring and pharmacokinetic strategies for managing initiation of gentamicin in newborns after maternal ODD gentamicin. Further studies are warranted to evaluate the effects of maternal ODD of gentamicin on newborns and the optimal therapeutic drug monitoring strategy.

## Article Information

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**Ethical Approval and Informed Consent.** This project received a formal Determination of Quality Improvement status according to University of Chicago Medicine institutional policy. As such, this initiative was deemed not human subjects research and was therefore not reviewed by the Institutional Review Board.

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