



Article

Perinatal Antibiotic Timing Impairs Maternal IgG Transfer via FcRn and Shapes the Neonatal Gut Microbiome in Mice

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Abstract

Perinatal antibiotic exposure poses a significant risk to maternal-offspring immune programming and infant gut microbiota development. This study investigated the time-specific effects of maternal cefoperazone sodium (CPZ) administration on IgG transfer and offspring gut microbiota in a murine model. Pregnant C57BL/6J mice were assigned to control (CON), gestational (G-CPZ), lactational (L-CPZ), and combined gestational/lactational (GL-CPZ) treatment groups. Results showed that all CPZ treatments significantly reduced IgG and its subtype levels in maternal serum, colostrum, and offspring serum ($p < 0.05$). Concurrently, mRNA expression of the neonatal Fc receptor (FcRn), critical for IgG transport, was downregulated in both maternal breast and offspring intestinal tissues ($p < 0.05$). Furthermore, 16S rRNA sequencing revealed that CPZ exposure altered offspring gut microbiota diversity and composition. Alpha diversity was reduced, particularly in the G-CPZ group, while beta diversity showed significant separation in L-CPZ and GL-CPZ groups ($p < 0.05$). Taxonomic shifts included decreased Bacteroidetes and Lactobacillus, and in the GL-CPZ group, a marked increase in Firmicutes and potential pathobionts like *Enterococcus* and *Hungatella* ($p < 0.05$). These findings demonstrate that perinatal antibiotic exposure, depending on its timing, impairs maternal-offspring IgG transfer via the FcRn pathway and induces distinct, persistent alterations in the offspring's gut microbiota, which may have implications for neonatal immunity and long-term health.

Keywords: perinatal antibiotic; IgG transfer; FcRn; gut microbiota; neonatal immunity



Academic Editor: Denis Roy

Received: 25 December 2025

Revised: 20 January 2026

Accepted: 22 January 2026

Published: 24 January 2026

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1. Introduction

The perinatal period represents a critical window for the establishment of the neonatal immune system and gut microbiota, both of which are profoundly regulated by maternal factors [1,2]. Immunoglobulin G (IgG), transferred from mother to offspring via the placenta and colostrum/milk, serves as the primary route for neonates to acquire humoral immunity, providing essential protection against pathogens during early life. This transfer is predominantly mediated by the neonatal Fc receptor (FcRn) [3]. Concurrently, the early colonization of the gut microbiota, crucial for host metabolic programming, immune education, and barrier function, is highly susceptible to environmental disturbances [4,5].

Antibiotics are among the most common medical interventions during the perinatal period [6,7]. While effective in controlling infections, their off-target effects on commensal microbiota and host physiology have raised increasing concern. Cefoperazone is a

third-generation cephalosporin. In clinical practice, particularly when combined with the β -lactamase inhibitor sulbactam, it is a commonly used agent for treating Gram-negative bacilli infections. Owing to its broad-spectrum antibacterial activity, it is frequently employed as a standard agent for establishing animal models of antibiotic-induced gut microbiota dysbiosis. Maternal antibiotic use may disrupt the maternal microbiome, thereby interfering with the vertical transmission of beneficial microorganisms and affecting IgG absorption via the modulation of FcRn expression, ultimately altering the immunological composition of milk [8,9]. Microbes can influence FcRn-mediated IgG absorption, with FcRn being the sole receptor specifically responsible for IgG transport in neonates. Furthermore, the impact of perinatal antibiotic exposure exhibits distinct stage-specificity, where different exposure timings lead to differential maternal and infant outcomes. Studies have found that administering antibiotics before skin incision (prior to delivery) during cesarean section specifically impairs the early colonization of neonatal gut Bifidobacteria [10]. Additionally, for pregnant women with premature rupture of membranes at 24–31 weeks of gestation, the use of ceftriaxone instead of amoxicillin significantly improves the proportion of neonates surviving without major morbidities [11]. However, how the timing of antibiotic exposure, specifically during gestation, lactation, or both, affects the coordinated axis of maternal IgG transfer (mediated by FcRn) and offspring gut microbiota assembly remains poorly understood.

To elucidate the temporal impact of maternal cefoperazone sodium exposure, this study aimed to assess its effects on three key parameters: IgG and subtype levels in maternal serum, milk, and offspring serum; the expression of pivotal genes (FcRn, TLR4, TLR2) involved in IgG transport and intestinal immune sensing within mammary and offspring intestinal tissues; and the structural composition and diversity of the offspring's gut microbiota. We further hypothesized that perinatal antibiotic exposure disrupts the FcRn-mediated IgG transfer pathway in a stage-specific manner, concurrently driving distinct patterns of gut dysbiosis in the offspring.

2. Materials and Methods

2.1. Materials

The cefoperazone sodium sample (purity > 98%) was purchased from Shanghai Yuanye Biotechnology Co., Ltd. (Shanghai, China).

2.2. Animals and Treatments

Based on our prior research [9], a total of 32 pregnant C57BL/6J mice at 12 weeks of gestation were obtained from Henan Scribes Biotechnology Co., Ltd. (Zhengzhou, Henan, China) and randomly assigned into four groups: control (CON), gestational antibiotic treatment group (G-CPZ), lactational antibiotic treatment group (L-CPZ), and combined gestational and lactational antibiotic treatment group (GL-CPZ). The G-CPZ group received drinking water containing 0.5 mg/kg cefoperazone sodium from gestational day 15 until the day of delivery; the L-CPZ group received the same antibiotic-supplemented water from the day of delivery until lactation day 14; and the GL-CPZ group received the treatment from gestational day 15 through lactation day 14 (Figure 1).

2.3. Serum and Milk

At lactation day 14, the dam and offspring were anesthetized. Blood samples were obtained through retro-orbital sinus bleeding, after which all animals were euthanized. Blood was collected via retro-orbital bleeding into centrifuge tubes. Following collection, samples were allowed to clot at room temperature for 15 min and then centrifuged at $3000 \times g$ for 15 min to separate serum. The serum was aliquoted and stored at -80°C for

subsequent IgG and subtype quantification. For milk antibody analysis, stomach contents from pups were homogenized with ultrapure water (1:4, *v/v*). The homogenate was centrifuged at $3500\times g$ for 10 min, and the supernatant was collected for measurement. Levels of IgG, IgG1, IgG2b, and IgG3 in both serum and milk supernatants were determined using commercial ELISA kits (Jiangsu Meibiao Biotechnology Co., Ltd., Yancheng, China) strictly according to the manufacturer's protocols.

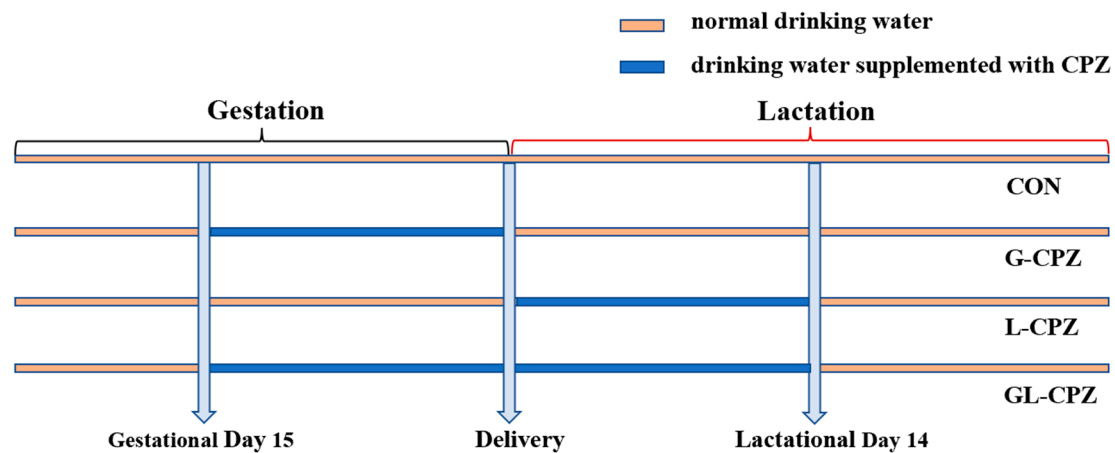


Figure 1. Design of the Animal Experiment.

2.4. Real-Time Quantitative PCR

After the dams were euthanized, mammary gland tissue was harvested from the left inguinal fat pad. The collected tissue was placed in cryovials, rapidly frozen in liquid nitrogen, and transferred to a -80°C freezer for long-term storage pending RNA analysis. Total RNA was extracted from the tissue using the EasyPureTM RNA Kit (TransGen Biotech, Beijing, China). Subsequent cDNA synthesis was carried out with a corresponding reverse transcription kit (TransGen Biotech). Gene expression levels were quantified by real-time PCR on an ABI 7500 system (Thermo Fisher Scientific, Waltham, MA, USA) with SYBR Green dye. The specific primer sequences used are provided in Table 1.

Table 1. Primer sequences used for real-time quantitative PCR.

Genes	Primer Sequence (5'-3')
<i>GADPH</i>	F: AGGTCGGTGTGAACGGATTG R: TGTAGACCATGTAGTTGAGGTCA
<i>TLR4</i>	F: TCTGGGGAGGCACATCTTCT R: AGGTCCAAGTTGCCGTTTCT
<i>TLR2</i>	F: AGCCCATGAGAGGAAAGCC R: CCAAAACACTTCCTGCTGGC
<i>FcRn</i>	F: AAATGGTCAGAAGAGGGGGAC R: CCTCACCATTGAGGGCAAAC

2.5. Gut Microbiota

Cecal contents were collected from pups on lactation day 14. Full-length 16S rRNA gene sequencing was performed using the PacBio single-molecule real-time (SMRT) sequencing platform. The major procedures were as follows: Genomic DNA was extracted from cecal contents using the QIAamp Fast DNA Stool Mini Kit (Qiagen, Hilden, Germany), followed by quantification and quality assessment with Nanodrop (Thermo Fisher Scientific, Waltham, MA, USA) and Qubit (Thermo Fisher Scientific, Waltham, MA, USA).

The full-length 16S rRNA gene was amplified with universal primers 27F/1492R, and sequencing libraries were constructed using the SMRTbell Template Prep Kit (Pacific Biosciences, Menlo Park, CA, USA). Sequencing was subsequently carried out on a PacBio Sequel II system (Pacific Biosciences, Menlo Park, CA, USA) with the Sequel II Binding Kit (Pacific Biosciences, Menlo Park, CA, USA). Bioinformatic analysis included the following steps: raw reads were corrected using CCS software (Composer Studio™ v12.7.0, Pacific Biosciences) to generate high-quality consensus sequences; primer identification and deduplication were performed with Lima (Pacific Biosciences); chimeric sequences were removed via isoseq3 refine (Pacific Biosciences) to obtain high-quality non-chimeric sequences; operational taxonomic units (OTUs) were clustered at 97% similarity using the UCLUST algorithm; and taxonomic annotation was conducted against the SILVA database (release 138.1). All bioinformatic analyses were performed on the Paisenno Gene Cloud platform (Shanghai Paisenno Biotechnology Co., Ltd., Shanghai, China).

2.6. Statistical Analysis

Data are expressed as mean $\pm$ standard error of the mean (SEM). Statistical analyses were conducted based on the number of replicates per group. Differences among groups were assessed using one-way analysis of variance (ANOVA), followed by Duncan's post hoc test. Statistical significance was defined as $p < 0.05$.

3. Results

3.1. Effects of Time-Specific Maternal Antibiotic Treatment on Levels of IgG and Its Subtypes

Compared to the CON group, all antibiotic-treated groups markedly reduced IgG levels in maternal serum, colostrum, and pup serum ($p < 0.05$; Figure 2A,E,I). Relative to the CON group, the G-CPZ and GL-CPZ groups exhibited significant decreases in IgG1 levels in maternal serum, colostrum, and pup serum ($p < 0.05$; Figure 2B,F,J). In comparison with the CON group, the G-CPZ group showed a significant reduction in both IgG1 and IgG3 levels across maternal serum, colostrum, and pup serum ($p < 0.05$; Figure 2C,D,G,H,K,L).

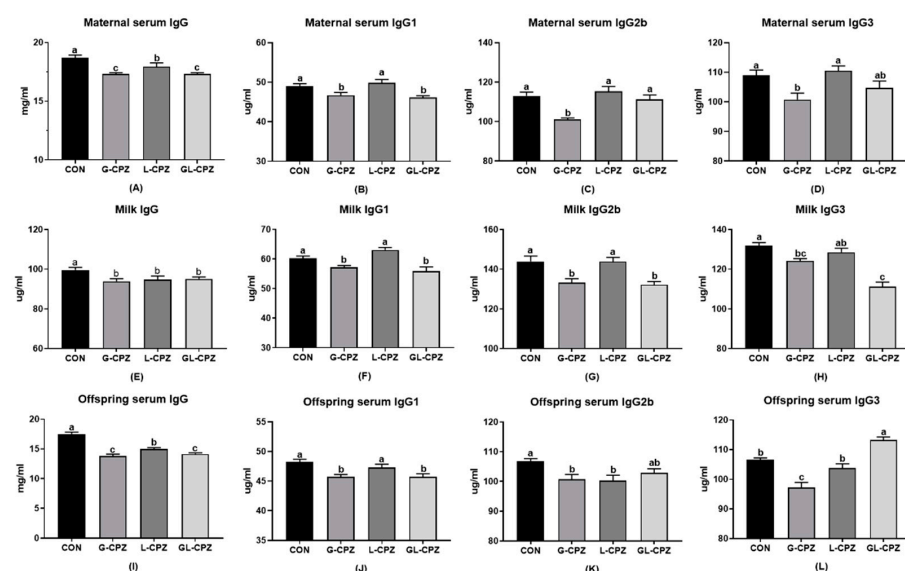


Figure 2. Antibiotic treatment impairs maternal-offspring transfer of IgG and subtypes. CON: Control group; G-CPZ: Group supplemented with CPZ during gestation; L-CPZ: Group supplemented with CPZ during lactation; GL-CPZ: Group supplemented with CPZ during gestation and lactation. (A–D) Maternal serum IgG, IgG1, IgG2b, IgG3 concentration; (E–H) Milk IgG, IgG1, IgG2b, IgG3 concentration; (I–L) Offspring serum IgG, IgG1, IgG2b, IgG3 concentration. Bars sharing a common letter are not significantly different, whereas those with different letters are significantly different ($p < 0.05$).

3.2. Effect of Time-Specific Maternal Antibiotic Treatment on IgG Transport-Related Gene Expression

In breast tissue of dams, both the L-CPZ and GL-CPZ groups showed significantly reduced FcRn mRNA expression, and the GL-CPZ group exhibited a marked decrease in TLR4 mRNA expression compared with the CON group ($p < 0.05$; Figure 3A,E,I). In the intestinal tissues of offspring mice, compared to the CON group, the G-CPZ, L-CPZ, and GL-CPZ groups significantly downregulated the mRNA expression of FcRn, TLR4, and TLR2 in both the duodenum and jejunum ($p < 0.05$; Figure 3B,C,F,G,J,K). In the ileum, the same three treatment groups significantly lowered FcRn mRNA levels ($p < 0.05$; Figure 3D) but had no significant effect on the expression of TLR4 or TLR2 mRNA ($p > 0.05$; Figure 3H,L).

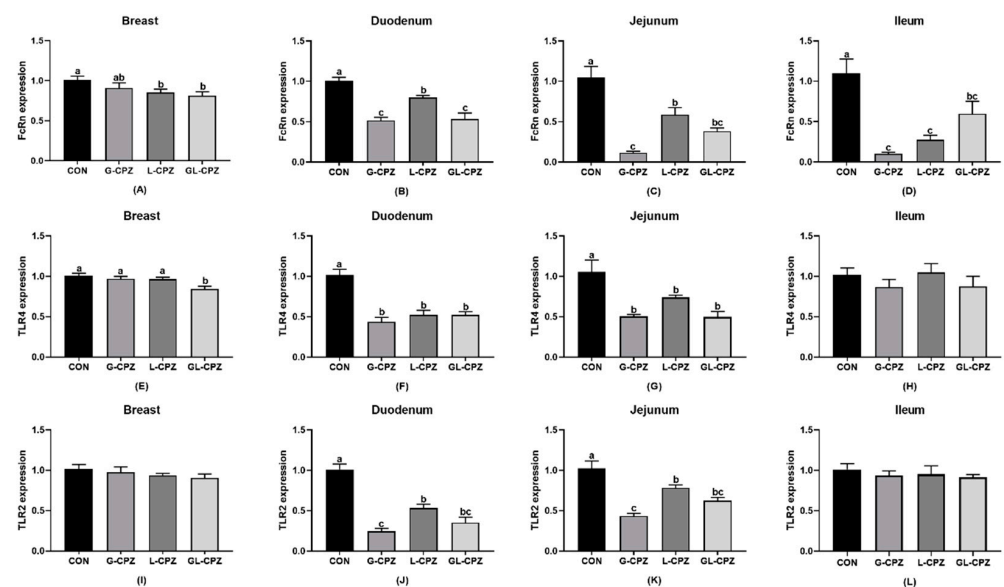


Figure 3. Perinatal antibiotic exposure downregulates FcRn and toll-like receptor expression in maternal breast and offspring intestine. (A) Breast FcRn mRNA expression; (B–D) Offspring duodenum, jejunum, ileum FcRn mRNA expression; (E) Breast TLR4 mRNA expression; (F–H) Offspring duodenum, jejunum, ileum TLR4 mRNA expression; (I) Breast TLR2 mRNA expression; (J–L) Offspring duodenum, jejunum, ileum TLR4 mRNA expression. Bars sharing a common letter are not significantly different, whereas those with different letters are significantly different ($p < 0.05$).

3.3. Effect of Time-Specific Maternal Antibiotic Treatment on Offspring Intestinal Microbiota

The impact of maternal antibiotic treatment on offspring gut microbiota is shown in the figure below. Regarding alpha diversity analysis, compared to the CON group, the G-CPZ group exhibited a significant reduction in the observed species index ($p < 0.05$; Figure 4A), and decreases ($p > 0.05$; Figure 4A) in the chao1, shannon, and simpson indices. Compared to the G-CPZ group, the L-CPZ and GL-CPZ groups showed remarkable reductions in the Simpson and Observed species indices ($p < 0.05$; Figure 4A). In terms of beta diversity analysis, PCoA revealed a significant separation between the CON group and the L-CPZ and GL-CPZ groups. For taxonomic composition analysis, compared to the CON group, all other experimental groups displayed a marked decrease in the relative abundances of Bacteroidetes, Verrucomicrobia, and *Lactobacillus* (*Lactobacillus murinus*). The GL-CPZ group demonstrated a significant increase in the relative abundances of Firmicutes, *Enterococcus* (*Enterococcus faecium*), *Hungatella* (*Hungatella hathewayi*), *Lachnoclostridium*, and *Flavonifractor* (*Flavonifractor plautii*) ($p < 0.05$; Figure 4D, Supplementary Tables S1–S3). In the analysis of differential species and biomarkers, LEfSe analysis identified the following sets of differential biomarkers: the CON group was characterized by *Muribaculum*, *Parabacteroides*,

Lactococcus, *Thiobacter*, and *Helicobacter*; the G-CPZ group by Verrucomicrobia, *Morganella*, *Proteus*, and *Akkermansia*; the L-CPZ group by *Sphigobacterium*, *Thermus*, *Enterococcus*, *Streptococcus*, *Ochrobactrum*, and *Paenaltcaligenes*; and the GL-CPZ group by Firmicutes, *Hungatella*, *Lachnoclostridium*, *Clostridioides*, and *Flavonifractor* (Figure 4E).

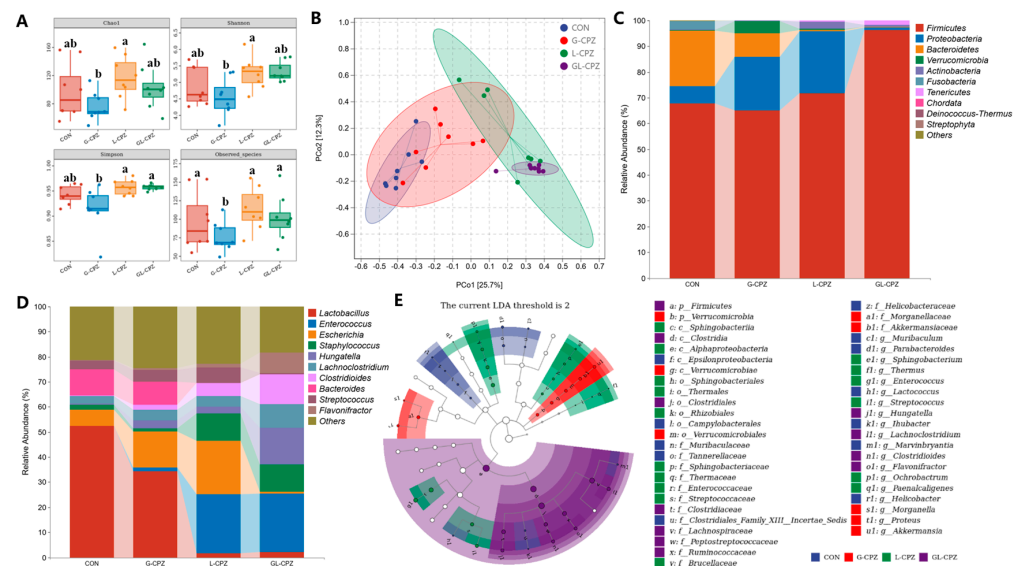


Figure 4. Maternal antibiotic exposure alters offspring gut microbiota diversity, structure, and taxonomic composition. (A) α diversity index; (B) PCoA clustering analysis; (C,D) Community taxonomic composition and abundance distribution map at the phylum and genus level; (E) LefSe analysis. Bars sharing a common letter are not significantly different, whereas those with different letters are significantly different ($p < 0.05$).

4. Discussion

The findings of this study demonstrate that perinatal cefoperazone sodium exposure significantly disrupted maternal-offspring IgG transfer and reshaped the offspring gut microbiota in a time-dependent manner.

Firstly, we observed that all antibiotic treatment groups exhibited a significant reduction in the levels of IgG and its subtypes (IgG1, IgG2b, IgG3) in maternal serum, colostrum, and offspring serum. This systemic decrease coincided with the downregulation of FcRn mRNA expression in both maternal mammary tissue and offspring intestinal tissues (duodenum and jejunum) [12–14]. FcRn is the key receptor responsible for trans-epithelial IgG transport. The reduced expression of this receptor likely directly compromised the efficiency of IgG transfer. It affected both the transfer from the maternal circulation into milk and the transfer from the offspring's intestinal lumen into the bloodstream. Our prior research also indicated that gestational antibiotic-induced dysbiosis (e.g., reduction in beneficial bacteria) might lead to downregulated FcRn mRNA expression, thereby impairing intestinal IgG transport in offspring mice [9]. It is noteworthy that significant downregulation of FcRn in mammary tissue was observed only in the lactation (L-CPZ) and full perinatal exposure (GL-CPZ) groups, a pattern distinctly different from that in the gestational exposure (G-CPZ) group, where the primary effect was a reduction in maternal serum IgG levels. This finding carries important physiological implications: the high expression of FcRn in lactating mammary epithelium is the molecular basis for the IgG enrichment in milk [15]. Our results suggest that antibiotics may directly or indirectly interfere with this precisely regulated process during this critical period. This “window effect” aligns with clinical observations that maternal medication use during the postpartum lactation period has more direct potential effects on the infant. Furthermore, it is notable

that the expression of FcRn and TLRs (TLR4, TLR2) in the offspring intestine was also broadly suppressed. This indicates that the impact of antibiotics is systemic, extending beyond the dam. When combined with the observed microbial dysbiosis, this scenario constitutes a risk for immune deficiency [16–18].

Secondly, antibiotics can induce dysbiosis of the gut microbiota, even at very low doses [19]. Gut microbiota analysis revealed differential outcomes associated with the timing of antibiotic exposure. Gestational exposure (G-CPZ) primarily affected the alpha diversity of the microbiota (e.g., the Observed species index), indicating that antibiotics administered to the mother prenatally impacted the richness of the microbial seed bank transmitted to the offspring. Related experiments have also found similar results; for instance, Šumilo et al., through analyses such as structural equation modeling, confirmed a significant association between antibiotic exposure in the third trimester of pregnancy and a reduction in alpha diversity indices (e.g., the shannon index) of the neonatal gut microbiota [20]. Miyoshi et al. found that maternal antibiotic contact during pregnancy can induce dysbiosis in the maternal microbiome, and this dysbiosis can be transmitted to the offspring [21]. In contrast, lactational exposure (L-CPZ and GL-CPZ) induced more profound changes in beta diversity, suggesting that the lactation period (via milk composition and direct ingestion) is a critical phase shaping the early structural development of the offspring microbiota. This notion is supported by corroborating evidence: Ferretti et al., through a longitudinal metagenomic analysis of 195 mother-infant dyads, discovered that the breast milk microbiome significantly influences the species composition and community structure (i.e., beta diversity) of the infant gut microbiota via strain-level vertical transmission [22]. Salas-López et al. found that breast milk (colostrum) and neonatal feces exhibited homogeneity in core archaeal composition and beta diversity, hinting at microbial vertical transmission through breastfeeding [23]. Regarding taxonomic composition analysis, all treatment groups led to a decrease in the abundance of beneficial phyla such as Bacteroidetes and specific species like *Lactobacillus murinus* [24]. Notably, the GL-CPZ group (i.e., the full perinatal exposure group) exhibited the most significant features of dysbiosis. Specifically, its Firmicutes/Bacteroidetes ratio increased. Meanwhile, the relative abundance of potential pathogens or opportunistic pathogens (such as *Enterococcus faecium* and *Hungatella hathewayi*) also rose significantly. This microbial profile is considered to be associated with a pro-inflammatory state and an elevated risk of metabolic disorders [25,26]. These findings indicate that antibiotic exposure during both gestation and lactation exerts detrimental effects on offspring to varying degrees. Notably, perinatal antibiotic exposure exhibits an “accumulative effect”; intervention spanning the entire pregnancy and lactation period delivers the most detrimental blow to the establishment of a healthy microbiota in offspring, potentially rendering them the highest-risk cohort for future immune and metabolic disorders. Our findings link two critical pathophysiological processes: impaired FcRn-mediated passive immunity and gut microbiota dysbiosis. Antibiotics may disrupt the microbiota through direct microbial killing or indirect alteration of the host intestinal environment (e.g., inflammation, metabolites) [27]. In turn, the disrupted microbiota and its products (e.g., lipopolysaccharide) may further affect the expression and function of intestinal epithelial FcRn, potentially creating a vicious cycle [28,29].

While this study reveals the differential impacts of perinatal antibiotic exposure timing on maternal-fetal immune transfer and offspring microbiota, several important limitations should be considered when interpreting the findings. First, the inherent limitations of the animal model necessitate caution in directly extrapolating the results to human clinical contexts. Differences between mice and humans in placental structure, lactation patterns, and the timeline of immune system development exist. Furthermore, the use of a single antibiotic (cefoperazone sodium) in this study means its effects may not be representative

of other antibiotic classes or combination therapies. Second, the temporal scope and observational endpoints of the study are limited. All analyses were conducted during the early life of the offspring (e.g., at the end of the lactation period), precluding investigation into how these early immune and microbial alterations affect long-term health outcomes, such as susceptibility to infections, risk of allergic diseases, or metabolic disorders. Additionally, the depth of mechanistic exploration requires further strengthening. We measured FcRn mRNA levels but lack direct validation of protein expression, subcellular localization, and its transport function. Similarly, the failure to concurrently measure key microbial metabolites (e.g., short-chain fatty acids, bile acids) limits the elucidation of potential pathways involved. Finally, although the sample size met the requirements for basic statistical analysis, it may have been underpowered for detecting certain subgroup effects or changes in rare taxa. Future research should employ functional experiments to validate causal relationships, establish equivalent dose models across species to enhance clinical relevance, and conduct long-term longitudinal cohorts to assess the long-term consequences of early-life disturbances, thereby enabling a more comprehensive and accurate assessment of the potential risks associated with perinatal antibiotic exposure.

5. Conclusions

In conclusion, this study provides compelling evidence that the timing of perinatal antibiotic exposure is a critical determinant of its impact on neonatal immune acquisition and gut microbiome development. We demonstrate that cefoperazone sodium exposure, particularly during lactation or the entire perinatal period, disrupts the FcRn-mediated transfer of maternal IgG to offspring and induces distinct, potentially detrimental alterations in the offspring gut microbiota, characterized by reduced diversity and enrichment of pathobionts. These findings highlight that the perinatal period is one of heightened vulnerability and underscore the importance of carefully considering the timing and necessity of antibiotic administration during pregnancy and lactation.

Supplementary Materials: The following supporting information can be downloaded at <https://www.mdpi.com/article/10.3390/microorganisms14020276/s1>, Table S1: Effects of maternal CPZ treatment on gut microbiota composition in offspring mice (phylum level); Table S2: Effects of maternal CPZ treatment on gut microbiota composition in offspring mice (genus level); Table S3: Effects of maternal CPZ treatment on gut microbiota composition in offspring mice (species level).

Author Contributions: Conceptualization, Y.D.; methodology, Y.D., A.L. and B.M.; formal analysis, C.Z., J.L., A.L. and J.H.; investigation, C.S. and J.H.; data curation, J.H. and C.S.; writing—original draft preparation, Y.D., J.H. and C.S.; writing—review and editing, Y.D.; visualization, J.H.; supervision, C.S.; project administration, Y.D.; funding acquisition, Y.D., B.M., J.L. and H.Z. All authors have read and agreed to the published version of the manuscript.

Funding: This work was supported by the Doctoral Research Fund of Shangqiu Normal University (SQNUQDF2544), Natural Science Foundation of Henan Province of China (252300420717), Key scientific research project of colleges and universities in Henan Province (25CY029, 24A310009), Cultivation Project of International Science and Technology Cooperation (252102520023).

Institutional Review Board Statement: The animal study protocol was approved by the Laboratory Animal Ethics Committee of Shangqiu Normal University of Commerce, with the number SQNU-20250102, approval date: 2 January 2025.

Informed Consent Statement: Not applicable.

Data Availability Statement: The original contributions presented in this study are included in the article and Supplementary Materials. Further inquiries can be directed to the corresponding authors.

Conflicts of Interest: The authors declare no conflicts of interest.

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