

Emergence of ST1193 Clone in Maternal and Neonatal ESBL-Producing *E. coli* Isolates

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Objective: The emerging epidemic of extended-spectrum β -lactamase-producing *E. coli* (ESBL-EC) is a global public health crisis. ESBL-EC infections are increasing worldwide and contribute to morbidity and mortality among newborn infants. However, the antimicrobial resistance characteristics and clonal transmission of maternal and neonatal ESBL-EC isolates need to be further deciphered.

Materials and Methods: We performed phenotypic and genotypic characterization of 33 ESBL-EC isolates from pregnant women and newborn during 2019–2020.

Results: Minimum inhibitory concentrations of 17 antimicrobial agents showed that all isolates were multidrug-resistant (MDR) and had a resistance rate of 100% to ampicillin, and mild resistance to florfenicol, gentamicin, ceftazidime, and amoxicillin-clavulanate. Additionally, imipenem, meropenem, polymyxin, and tigecycline exhibited good activity against the tested ESBL-EC isolates with low MIC₅₀ (0.06–1 μ g/mL) and MIC₉₀ (0.06–1 μ g/mL). Whole genome sequencing indicated that ESBL-EC isolates contained diverse antimicrobial resistant genes (*bla*_{CTX-M}, *bla*_{TEM}, *bla*_{SHV}, *tetA*, etc.) and toxin genes (*ompA*, *csg*, *fimH*, *hybA*, etc.). *bla*_{CTX-M} genes were the main ESBL genotype. ST1193 (18.2%) was the second most abundant ST among the ESBL-EC isolates (ST131 was the most common, with 30.3%), and this is the first report of its mother-to-infant colonization transmission in China.

Conclusion: These findings revealed the occurrence of high-risk ST1193 clone among ESBL-EC isolates from pregnant women and newborn colonization in China. Further national or regional multicenter studies are needed to assess the dissemination and evolution of ESBL-EC ST1193 clone as a nosocomial pathogen in China.

Keywords: ESBL, *E. coli*, antibiotic resistance, colonization transmission, ST1193 clone

Introduction

Extended-spectrum β -lactamase *Enterobacteriaceae* is an important public health threat of widespread clinical concern, with increasing infection rates resulting in increased neonatal mortality.¹ Extended-spectrum β -lactamase-producing *Escherichia coli* (ESBL-EC) are the largest group of multidrug-resistant pathogens in obstetric bacteraemia.^{2,3} ESBL-EC infections are responsible for an estimated 14,000 healthcare-associated infections annually in the United States.⁴ ESBL-EC infections may lead to poor treatment outcomes, lower rates of clinical and microbiological response, prolonged hospitalization, and higher hospital costs.^{5,6}

Since ESBL-EC can spread antimicrobial resistance among different bacteria in many ways, it is easy to cause the epidemic of antimicrobial resistant bacteria. Neonatal infection by ESBL-EC may be associated with higher fatality rates, colonized mothers may be a source of neonatal transmission.⁷ Maternal colonization with ESBL-EC is considered as a significant risk factor for the acquisition of neonatal infection.^{8,9} Fecal carriage of ESBL-EC is an important reservoir for the transmission and dissemination of infection with resistant strains.¹⁰ Previous studies on clinical patients found that

fecal carriage appeared to be common several months after ESBL-EC infection.^{11,12} In Europe, fecal carriage rate of AmpC β -lactamase genes (*bla*_{CMY-2} and *bla*_{DHA-1}) in the community was approximately 10%.¹³ Due to the high number of maternal and infant colonization associated with infections caused by these bacteria, the World Health Organization classifies *Enterobacteriaceae* as priority organisms for which new antimicrobials drugs are urgently needed.¹⁴ β -lactam antimicrobials have become the first-line antibacterial drugs for humans because of their high potency, broad antibacterial spectrum, and minimal side effects.¹⁵ ESBL-producing microorganisms exhibit co-resistance to many other classes of antibiotics and carry additional resistance genes, which limit therapeutic options. Inevitably, the problem of ESBL-producing antimicrobial resistance poses great threat to the treatment of clinical infections.

ESBLs are plasmid-encoded enzymes produced by *Enterobacteriaceae* that induce bacterial resistance by hydrolyzing β -lactam antibiotics.^{16,17} Currently, hundreds of ESBLs have been identified. *bla*_{TEM}, *bla*_{SHV}, and *bla*_{CTX-M} are the common genotypes. CTX-M ESBLs are predominantly found in isolates from community-acquired infections,¹⁸ where the CTX-M-15 variant is the most common enzyme. The widespread use of third-generation cephalosporins and aztreonam is believed to be the major cause of mutations in these enzymes which has led to the emergence of the ESBLs. In addition, sequence type 131 (ST131) has been shown to contribute to the global spread of CTX-M-producing *E. coli*.¹⁹ Recently, ST1193 constituted an emerging fluoroquinolone-resistant *E. coli* clone in clinic.^{20,21} It is well known that the epidemiology of maternal-neonatal colonization has found that certain species or ST groups are more likely to harbor resistance or virulence determinants.^{22,23} Therefore, a comprehensive analysis of antibiotic resistome of ESBL-EC isolated from pregnant women and newborn could decipher the spread of molecular transmission. To investigate the prevalence and molecular characteristics of maternal and neonatal ESBL-EC isolates in Beijing, China, we evaluated the molecular profiles, including STs, phylogroups, and antibiotic resistome of ESBL-EC strains. We clarify the associations between phenotypic and genotypic data and demonstrate the presence of diverse antibiotic resistome in maternal and neonatal ESBL-EC.

Materials and Methods

Bacteria Isolate

We studied maternal and neonatal samples collected from the Beijing Obstetrics and Gynecology Hospital affiliated to Capital Medical University in Beijing, China (detailed descriptions of the patients were given in [Table S1](#)). All clinical samples (throat swab, placenta, perineum incision, blood, urine, or cervical secretion) were inoculated onto selective chromogenic medium ESBL-E (CHROMagarTM ESBL, France) and incubated in ambient air at 37°C for 24 h. Individual colonies were then sub-cultured onto blood agar plates. Species confirmation was performed using an API20E system (bioMérieux) and matrix-assisted laser desorption ionization-time of flight mass spectrometry (MALDI-TOF/MS) (Bruker, Germany). ESBL production was confirmed using the combined disc diffusion method according to the Clinical and Laboratory Standard (CLSI) guidelines.²⁴ The production of ESBL was confirmed by an increase in the diameter of the zone tested with cefotaxime/clavulanate or ceftazidime/clavulanate relative to when tested alone by ≥ 5 mm.²⁵

Antimicrobial Susceptibility Test

A total of 33 well-grown maternal and neonatal ESBL-EC isolates were selected for antimicrobial susceptibility test. The agar dilution method was used to determine their susceptibility to 17 antimicrobial agents, including imipenem, meropenem, cefepime, cefotaxime, ceftazidime, cefoxitin, tigecycline, tetracycline, polymyxin B, colistin, ampicillin, amoxicillin-clavulanate, amikacin, kanamycin, gentamicin, ciprofloxacin, and florfenicol. Antimicrobial susceptibility test was performed in accordance with the guideline of CLSI documents M100-S30.²⁴ *E. coli* ATCC 25922 was used as a quality control. Minimum inhibitory concentrations (MICs) for susceptibility (S), intermediate susceptibility (I) and resistance (R) were defined according to the recommendations of the European Committee on Antimicrobial Susceptibility Testing (EUCAST).²⁵

Whole Genome Sequencing

Genomic DNA was extracted from ESBL-EC strains using the Wizard Genomic DNA Purification Kit (Promega, Madison, WI, US). Then, DNA libraries were constructed using the KAPA Hyper Prep Kit (Roche, Basel, Switzerland). Genomic sequencing was performed using the Illumina Novaseq 6000 platform (Illumina, San Diego, CA), which generated 150-bp

paired-end reads from the libraries with an average insert size of 350 bp. For each isolate, >550 M bp of high-quality clean reads were obtained and assembled de novo using SPAdes v.3.10²⁶ by default settings and *k*-mer sizes ranging from 21 to 127. Multi-locus sequences were identified using the pMLST 2.0 database. Antimicrobial resistance and toxin genes were identified using the SRST2 Toolkit (version 0.2.0, University of Melbourne, <http://katholt.github.io/srst2/>). All genome drafts were used to construct a phylogenetic tree using the parsnp software,²⁷ and the trees were finally visualized using the online tool iTOL (<http://itol.embl.de/>).

Results

Epidemiology of Isolates

We included all 33 ESBL-EC isolates in this study and the isolates were submitted from maternal and newborn patients in Beijing. The isolates were collected from a variety of sources: 9 from neonatal carriage (7 isolates from throat swabs and 2 isolate from neonatal bloodstream infection), 24 from pregnant women (16 isolates from placenta, 3 isolates from perineum incision, 3 isolates from blood, 1 strain from cervical secretions, and 1 isolate from urine).

Phenotypic Characterization of ESBL-EC Isolates

The distributions of MICs and test concentrations of different antibiotics against the tested 33 isolates are summarized in Table 1. Among the tested antibiotics, high proportion of resistance to ampicillin (*n* = 33, 100.0%), cefotaxime (*n* = 30, 90.9%), tetracycline (*n* = 28, 84.85%) was observed, with MIC₉₀ in all above the dilution ranges (>128 µg/mL, >16 µg/mL, >64 µg/mL, respectively). Mild resistance was observed to gentamicin (21.21%), florfenicol (18.18%), ceftazidime (30.3%), and amoxicillin-clavulanate (12.12%). However, almost all the tested ESBL-EC isolates exhibited low-level resistance to kanamycin (3.03%), cefepime (3.03%), and ceftoxitin (9.09%). We found that colistin, polymyxin B, tigecycline, amikacin, imipenem and meropenem showed good antimicrobial activity against these ESBL-EC isolates with low MIC₅₀ (0.06–1 µg/mL) and MIC₉₀ (0.06–1 µg/mL) (Figure 1A). Overall, ampicillin-tetracycline-cefotaxime was the most frequently observed antimicrobial resistance profile.

Antibiotic Resistome Characterization of ESBL-EC Isolates

We confirmed the presence of the ESBL genes in each isolate by using WGS. β-lactam resistance genes were observed in all isolates, which verified our ESBL phenotypic screen (Figure 2). Among the 33 ESBL-producing *E. coli* strains, 28 strains (84.85%) carried the *bla*_{CTX-M} genes, 10 strains (30.30%) carried the *bla*_{TEM} genes, and 4 strains (12.12%) carried the *bla*_{SHV} genes. In addition to the three most common β-lactamase genes, *bla*_{CMY-2}, *bla*_{OXA}, and *bla*_{DHA} were also observed. The most prevalent *bla*_{CTX-M} genes detected were *bla*_{CTX-M-27} (15/33, 45.45%), *bla*_{CTM-M-14} (7/33, 21.21%), *bla*_{CTM-M-55} (3/33, 9.09%), and *bla*_{CTX-M-15} (3/33, 9.09%) (Figure 1B). The ESBL-EC isolates were classified into 14 different STs, with the predominant STs being ST131 (*n* = 10, 30.3%) ST1193 (*n* = 6, 18.2%), followed by ST69 (*n* = 3, 9.1%). The rest (11 STs) occurred in one isolate each. Interestingly, a new globally emerging clone ST1193 in ESBL-EC was identified in 6 maternal and neonatal isolates. Among the ST1193 isolates, the most common resistance genes included *bla*_{CTX-M-27} (β-lactam resistance) and *dfrA17* (trimethoprim resistance). Notably, we found that maternal-neonatal colonization transmission was found in the ST1193 clone strains.

A total of 11 additional resistant genes were detected followed by the β-lactam resistance genes. The detection rate of tetracycline-resistant gene *tetA* presented was the highest (66.67%), followed by another tetracycline-resistant gene *tetB* (18.18%). Furthermore, sulfonamide-resistant genes *sul1* and *sul2* were conserved in 48.48% and 60.61% of the isolates, respectively. The most common aminoglycoside-resistant genes were *aadA5* (45.45%), *strA* (54.55%), *strB* (54.55%), and *aac* (3) (21.21%), respectively. Notably, several isolates were found to carry the amphenicol-resistant gene *floR* (*n* = 3), fluoroquinolone resistant genes *qnr* (*n* = 6) and *oqx* (*n* = 1) (Figure 1C).

Then we analyzed the genetic context of ESBL-EC isolates by examining the contigs to determine the chromosomal or plasmid environment. Isolates 5, 6, and 11 (carrying *bla*_{TEM-1B}) were located on the IncF plasmid, and the regulatory genetic element IS1 was located the downstream of *bla*_{TEM-1B}. Isolates 5 and 6 (carrying *bla*_{CTX-M-55}) also contained the IncI1 plasmid and ISEcp1 was located the upstream of *bla*_{CTX-M-55} (Figure 1D).

Table 1 MIC Distribution of 33 ESBL-Producing *E. coli* Isolates Against 17 Antimicrobial Agents

Antimicrobial Agents	Number of Isolates for Different MICs ($\mu\text{g/mL}$) ^a																MIC50 ^b	MIC90 ^c	Resistant Isolate (%R)	Intermediate Isolate (%I)	Sensitive Isolate (%S)
	0.015	0.03	0.06	0.125	0.25	0.5	1	2	4	8	16	32	64	128	256	512					
IMI			16	11	5		1										0.125	0.25	0(0.00)	0(0.00)	33(100.00)
MERO			32	1													0.06	0.06	0(0.00)	0(0.00)	33(100.00)
FEP	1		2			1	9	12	6	1	1						2	4	1(3.03)	1(3.03)	31(93.94)
CTX					1			2	3		13	14					16	32	30(90.91)	2(6.06)	1(3.03)
CAZ				1	1	3		1	7	10	3	5	2				8	32	10(30.30)	17(51.52)	6(18.18)
FOX								2	23	5		1	1	1			4	8	3(9.09)	5(15.15)	25(75.76)
TGC					7	18	8										0.5	1	0(0.00)	0(0.00)	33(100.00)
TET							2	1	1	1			6	16	6		128	256	28(84.85)	2(6.06)	3(9.09)
POL				1	22	10											0.25	0.5	0(0.00)	0(0.00)	33(100.00)
COL				2	25	5	1										0.25	0.5	0(0.00)	0(0.00)	33(100.00)
AMP														2	1	30	512	>512	33(100.00)	0(0.00)	0(0.00)
AMC										16	13	1	3				16	32	4(12.12)	13(39.39)	16(48.48)
AMI						24	6	3									0.5	1	0(0.00)	0(0.00)	33(100.00)
KAN							1	24	4	1	2				1		2	4	1(3.03)	2(6.06)	30(90.91)
GEN					2	6	10	7	1		1		4	2			1	64	7(21.21)	0(0.00)	26(78.79)
CIP				12	6	2					1	11	1				0.25	32	13(39.39)	20(60.61)	0(0.00)
FFC									13	14	2			1	3		8	256	6(18.18)	14(42.42)	13(39.39)

Notes: ^aThe unshaded fields denote the dilution range of the agar plates used to test isolates. Values beyond this range indicate MIC equal to higher/lower than the tested concentrations. ^bMIC₅₀, MIC at which 50% of isolates were inhibited by a specific antimicrobial. ^cMIC₉₀, MIC at which 90% of isolates were inhibited by a specific antimicrobial.

Abbreviations: CIP, ciprofloxacin; COL, colistin; POL, polymyxin B; TGC, tigecycline; TET, tetracycline; AMI, amikacin; GEN, gentamicin; KAN, kanamycin; FFC, florfenicol; IMI, imipenem; MERO, meropenem; FEP, cefepime; CTX, cefotaxime; CAZ, ceftazidime; FOX, ceftiofur; AMP, ampicillin; AMC, amoxicillin-clavulanate.

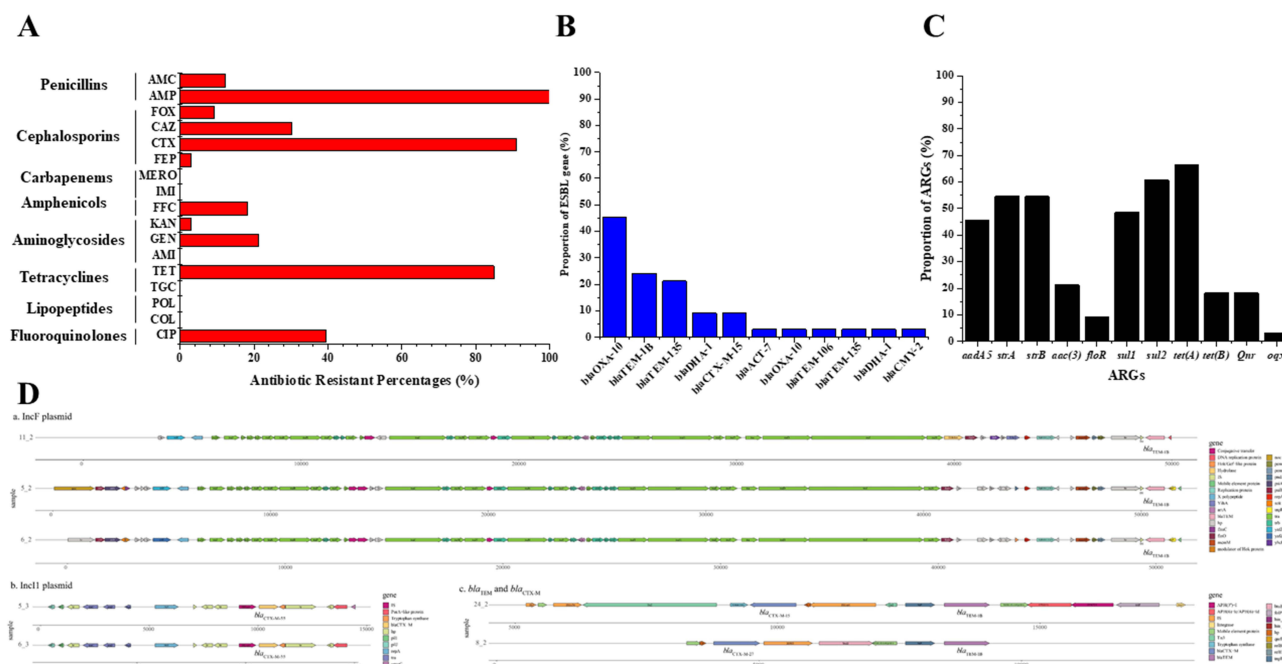


Table 2 Virulence Genes Carried by All the 33 ESBL-EC Isolates

Toxin Type	Virulence Gene	No.	Prevalence (%)
Membrane protein	<i>ompA</i>	33	100
Enterobactin biosynthetic enzymes	<i>ent</i>	32	97.0
Curli nucleator protein	<i>csg</i>	32	97.0
Adherence	<i>fimH</i>	31	93.9
	<i>yag</i>	31	93.9
	<i>papB</i>	22	66.7
	<i>sfa</i>	2	6.0
	<i>ybtA</i>	27	81.8
High-pathogenicity island	<i>ybtA</i>	27	81.8
Iron repressible protein	<i>irp</i>	26	78.8
Heme absorption	<i>chu</i>	25	75.8
Plasmid-carried enterotoxin	<i>senB</i>	19	57.6
Secreted autotransporter	<i>sat</i>	16	48.5
T3SS effectors	<i>esp</i>	12	36.4
Vacuolating autotransporter	<i>vat</i>	9	27.3
Hemolysin	<i>hly</i>	2	6.0

Importantly, the high prevalence of *ybtA* among all ST1193 isolates was interesting, because this gene is correlated with the high-pathogenicity island on virulence.

Discussion

The increasing prevalence of ESBL in China poses great challenges to patients, clinicians, and public health.^{28,29} Over time, the rapid spread of antimicrobial resistance could lead to the emergence and evolution of dominant cloned strains. *E. coli* ST131 is a classic example of a successful human antimicrobial resistance (AMR) super-clone.³⁰ However, recent studies confirm that the emergence of ST1193 represents the only known large clonal expansion of *E. coli* isolates apart from the global spread of ST131 over the last two decades.^{20,31–33} This study reports the isolation of the ST1193 clone in ESBL-EC from pregnant women and newborn in China. Typically, ST131 is associated with *bla*_{CTX-M-15}, which is currently disseminated globally and identified as the most widespread CTX-M ESBL enzyme worldwide.³⁴ Unlike ST131, the six ST1193 clone from mothers and newborns all carried *bla*_{CTX-M-27}, which suggest that there might be a relationship of clonal propagation between them.

Phenotypic correlations are generally considered to reflect genotypic correlations. The association between the phenotype and genotype is important because it links together the effects of natural selection. Correlation analysis between genotype and phenotype is the main approach to explain the development of antimicrobial resistance. In this study, all isolates were phenotypically resistant to β -lactams and exhibited various resistant profiles, with all of them being resistant to at least one more antibiotic group, such as aminoglycosides, quinolones, and sulfonamides. The resistance rates of ESBL-EC strains were greater than 80% against the third-generation cephalosporins, cefotaxime, and tetracyclines (Figure 1A). It has been suggested that cefotaxime and tetracycline are not considered effective choices for the treatment of maternal and neonatal infections caused by ESBL-EC. As expected, the ESBL-EC had a high susceptibility rate to imipenem, meropenem, polymyxin, and tigecycline (100%), indicating that carbapenems and polymyxin are considered as last resort antibiotics for the treatment of ESBL-EC infections in China. Notably, the clinical use of colistin should be recommended as an alternative for the treatment ESBL-producing Enterobacteriaceae only when carbapenems cannot be utilized, but this recommendation must be considered carefully in order to avoid the development of bacterial resistance.^{35,36}

We identified 18 STs among 33 ESBL-EC isolates. The most abundant ST type was ST131 (30.3%), followed by ST1193 (18.2%). A recent study of major MLSTs associated with ESBL-EC harboring CTX-M-14, CTX-M-55, or CTX-M-15 genes in Chinese hospitals showed that the most common STs were ST131 (14.6%), ST1193 (7.9%), ST405 (6.6%), ST69 (6.3%), and ST648 (6.3%).^{33,37} The ST1193 isolates was 50% resistant to ciprofloxacin. All ST1193

isolates possess an IncF plasmid that is apparently deficient in plasmid transfer due to complete deletion of its transfer locus, which is consistent with the report by Johnson et al.³¹

The most common virulence factors in our study were *ompA*, *fimH*, and *ybtA*. *ompA* and *fimH* are relevant to the pathogenesis of neonatal meningitis by promoting the adhesion and invasion of human brain microvascular endothelial cells. Therefore, they may also play a role in the early stage of neonatal bacteremia pathogenesis, which likely involve in bacterial adhesion and invasion of epithelial barriers. Importantly, all ST1193 isolates contained the high pathogenicity island (HPI) virulence factor *ybtA*, a transcriptional regulator of the AraC-like family, and the iron master regulator Fur that controlled the transcriptional regulation of the four operons located within the HPI.³⁸ Furthermore, HPI was responsible for the synthesis, secretion, and uptake of the siderophore Yersinia, which was shown to be an important virulence determinant.

The present study has some limitations. Firstly, the study was conducted in a single center in Beijing, China, which may not be representative of the ESBL-EC situation in other regions or countries. Secondly, the sample size is relatively small (33 isolates), which may limit the generalizability of the findings. Thirdly, the study only focused on ESBL-EC isolates from pregnant women and infants and did not include other types of patients or bacteria. Lastly, the study did not investigate the clinical outcomes of the patients infected with ESBL-EC, which may be important for understanding the impact of this pathogen on public health.

Conclusions

This study revealed for the first time the occurrence of ST1193 and mother-to-infant colonization transmission in maternal and neonatal ESBL-EC isolates. There was a high ampicillin-tetracycline-cefotaxime resistance among these ESBL-EC isolates. The *bla*_{CTX-M} genes were the main ESBL genotype. All ST1193 clones carried *bla*_{CTX-M-27} and were loaded as IncF-type plasmids. In addition, our study demonstrated that the whole genome sequencing could be used to accurately predict antimicrobial resistance determinants and monitor the epidemiology of clinically significant nosocomial clones. The relationship of clonal propagation between *bla*_{CTX-M-27} and ST1193 clone remains to be further studied.

Ethical Approval

The studies involving human participants have been reviewed and ethical approval was approved by the Ethics Committee of the Beijing Obstetrics and Gynecology Hospital of Capital Medical University (No. 2023-KY-002-01). Written informed consent for participation was not required for this study in accordance with the national legislation and the institutional requirements. In this study, we investigated the transmission characteristics and antimicrobial resistance of the ESBL-EC strains isolated from patient samples (blood, urine, or incision secretions). The samples could not identify the patient's identity information, and did not involve the patient's personal privacy or commercial interests. The content of the article only analyzed the situation of the strain (including drug resistance and genotyping), and did not analyze the situation related to the patient. The risk of this study is minimal, and it is an investigation of the antimicrobial resistance of pregnant women and newborns infected with ESBL-EC strains. We believe that informed consent can be waived, and we also explained it in the ethical review report.

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Disclosure

The authors declare that they have no conflict of interest.

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