Shigellosis and Pregnancy in French Guiana: Obstetric and Neonatal Complications

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Abstract. *Shigella* is a major cause of dysentery worldwide. Only a few cases of shigellosis during pregnancy have been reported. However, the neonatal and obstetric complications are potentially severe. The objective of this study was to describe the obstetric and neonatal complications of shigellosis during pregnancy. We carried out a retrospective study of 37 cases of shigellosis diagnosed in pregnant women at the maternity unit of Saint-Laurent du Maroni Hospital in west French Guiana between 2000 and 2014. Shigellosis diagnosis was based on the detection of *Shigella* in stool cultures from pregnant women (34 patients) or in a neonatal sample collected immediately after delivery (three neonates). In addition to the classic symptoms of shigellosis—an association of diarrhea, fever, and abdominal pain—we observed uterine contractions before the completion of 37 weeks of gestation in 61% of patients ($N = 17/28$). Cervical changes were associated with uterine contractions in 82% of cases ($N = 14/17$); 25% of the patients at risk of preterm birth went on to give birth prematurely ($N = 3/12$). Three cases of mother-to-child transmission were observed. Episodes of shigellosis in pregnant women may trigger uterine contractions and changes to the cervix, potentially resulting in miscarriage or preterm birth.

INTRODUCTION

Shigella is a major cause of dysentery worldwide. A prospective multicenter study carried out between 2000 and 2004 on 600,000 people in six Asian countries (Bangladesh, China, Pakistan, Indonesia, Vietnam, and Thailand) showed that *Shigella* was isolated from the stools of 5% of subjects with diarrhea. However, mortality rates were falling, due to improvements in childhood nutritional status and more rapid access to primary care and antibiotics in these developing countries.¹

French Guiana is an administrative area under the French jurisdiction in a tropical environment. It has a young population of multiple ethnic origins. In 2012, almost 44% of the population was under the age of 20 years.² Enteric diseases are a major public health problem. The socioeconomic level of this area, lower than that in mainland France, and the difficulty obtaining clean running water in some areas contribute to the presence of *Shigella* in French Guiana.

Only a few cases of shigellosis during pregnancy have been reported. Markham and others provided the first description of a case of maternal septicemia associated with intrauterine infection.³ Armor and others described a case of chorioamnionitis at term associated with neonatal bacteremia and pneumonia.⁴ Rebarber and others described a case of shigellosis complicating premature membrane rupture and leading to congenital infection and preterm birth at 25 weeks and 6 days of gestation.⁵ Ruderman and others described a case of shigellosis due to *S. sonnei* during the immediate postpartum period, associated with asymptomatic neonatal bacteremia.⁶

We carried out a retrospective descriptive study of cases of shigellosis diagnosed in pregnant women. We aimed to describe the possible obstetric and neonatal complications and to determine the antibiotic resistance profiles of the isolates.

METHODS

We studied 37 cases of shigellosis diagnosed in pregnant women at the maternity unit of Saint-Laurent du Maroni

Hospital between 2000 and 2014. Shigellosis was diagnosed on the basis of maternal stool cultures for 34 patients and cultures of neonatal samples for three neonates (two stool cultures and one gastric sample). We searched the medical files of the patients to determine the clinical presentation of the episode of shigellosis, the way in which it was managed, whether any antibiotics were prescribed, and the occurrence of any obstetric, neonatal, or general complications. Hospitalization was defined as a stay in hospital for more than 24 hours. Management was considered to be ambulatory in all other cases. A risk of late miscarriage was defined as a combination of uterine contractions and cervical changes occurring between 14 and 22 weeks of gestation. A risk of preterm birth was defined as a combination of uterine contractions and cervical changes occurring between 23 and 37 weeks of gestation. Preterm birth was defined as delivery before the completion of 37 weeks of gestation. We collected biological tests to determine the blood formula, C-reactive protein concentration, blood ionogram, and creatinemia of the patients. For each positive bacteriological result for *Shigella*, we described the species of the isolate obtained and its susceptibility to antibiotics. The stools were used to inoculate selenite broth (Oxoid, Dardilly, France) and Hektoen and *Salmonella-Shigella* agar (BioMérieux®, Marcy-l'Etoile, France). We assessed the susceptibility of the *Shigella* isolates to 18 antibiotics with the VITEK 2 Compact system (BioMérieux) in accordance with the recommendations of the *Société Française de Microbiologie*. The isolates were typed with three polyvalent sera for the identification of the most frequent serotypes: a serum directed against indole-negative *Shigella dysenteriae* (Bio-Rad®, Hercules, CA) agglutinating serotypes 1, 3, 4, 5, and 6; an anti-*Shigella flexneri* serum (Bio-Rad) agglutinating the six serotypes of this subgroup; and a serum directed against *Shigella sonnei* (Bio-Rad). This study was carried out with the approval of the local ethics committee of the Saint-Laurent du Maroni Hospital.

RESULTS

Characteristics of the study population. The characteristics of the study population are summarized in Table 1. Term at diagnosis was between 9 weeks and 6 days of gestation and

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TABLE 1

Demographics, clinical presentation, and biological expression of the infection in the study population

	N (%)	(Minimum-max)	Mean $\pm$ SD
Demographics			
Age (years)		(16-44)	28.9 $\pm$ 7.6
Gravidity		(1-15)	5.8 $\pm$ 3.8
Parity		(0-12)	4.6 $\pm$ 3.5
Clinical presentation			
Term			
First trimester	2 (5)		
Second trimester	4 (11)		
Third trimester	22 (60)		
< 37 weeks			
Third trimester	9 (24)		
> 37 weeks			
Stools			
Bloody	8 (24)		
Mucoid	6 (18)		
Watery	17 (50)		
Presence of leukocytes	32 (94)		
Presence of blood	23 (68)		
Maternal fever ($> 38.5^{\circ}\text{C}$)	16 (43)		
Abdominal pain	6 (17)		
Biological expression			
Anemia (hemoglobin < 10.5 g/dL)	18 (53)	(6.7-14.9)	10.1 $\pm$ 1.9
C-reactive protein (> 5 mmol/L)	31 (100)	(8.1-132)	60.7 $\pm$ 34.7
Hyponatremia (< 126 mmol/L)	0 (0)	(128-141)	135.7 $\pm$ 3.2
Hypokalemia (< 2.5 mmol/L)	2 (6)	(1.9-3.8)	3.0 $\pm$ 0.4
Creatinemia (> 100 mmol/L)	0 (0)	(39-100)	61.3 $\pm$ 13.1

SD = standard deviation.

40 weeks and 4 days of gestation. Two patients were in the first trimester of pregnancy, four were in the second trimester, and 31 were in the third trimester (22 before 37 weeks of gestation and nine already beyond 37 weeks of gestation).

Clinical presentation and biological expression of the episodes of shigellosis. The clinical presentation and biological expression of the episodes of shigellosis are summarized in Table 1.

Diarrhea was present in 97% of cases ($N = 36/37$) and was associated with abdominal pain in 17% of cases ($N = 6/36$). Maternal fever (core temperature $> 38.5^{\circ}\text{C}$) was objectively documented in 43% of cases ($N = 16/37$). The stools of the mother were bloody in 24% of cases ($N = 8/34$), mucoid in 18%

of cases ($N = 6/34$), and liquid in 50% of cases ($N = 17/34$). None of the women had severe dehydration requiring intravenous fluid administration.

Course of the episodes of shigellosis. Thirty-three patients (89%) were hospitalized and four patients (11%) were managed as outpatients. The mean hospital stay was 4.8 days (standard deviation = 2.2 days). Antibiotic treatment was administered to 86% of the patients ($N = 32/37$). The treatment was initiated before the susceptibility test result was obtained and was based on a combination of amoxicillin and clavulanic acid in 66% of cases ($N = 21/32$), ceftriaxone in 25% of cases ($N = 8/32$), and amoxicillin, secnidazole, or ofloxacin in 9% of cases ($N = 3/32$). Four patients were treated empirically with an antibiotic to which the strain isolated from the stools was subsequently found to be resistant (in three cases, the isolate was resistant to the combination of amoxicillin and clavulanic acid, whereas the isolate from the remaining patient was resistant to amoxicillin alone). Once the results of the antibiogram became available, the treatment was switched to ceftriaxone in two of the patients infected with strains resistant to the amoxicillin and clavulanic acid combination. Seven patients were treated empirically with an antibiotic to which the infecting strains displayed intermediate susceptibility (amoxicillin/clavulanic acid in each case). Once the antibiogram results became available, the treatment was changed in four patients: to ceftriaxone in two cases and to ofloxacin and cefixime in one case each. The obstetric and neonatal complications are presented, by initial treatment, together with the obstetric complications as a function of term, in Table 2. No local or systemic complications were observed. No obstetric complications were observed in the two patients diagnosed during the first trimester of pregnancy. Two of the four patients diagnosed during the second trimester of pregnancy presented a risk of late miscarriage at 17 weeks and 5 days of gestation and at 22 weeks and 5 days of gestation. Tocolytic treatment was administered and the outcome was favorable. Three (14%) of the 22 patients diagnosed during the third trimester of pregnancy, at a term of less than 37 weeks of gestation, had uterine contractions in the absence of cervical changes, and 12 (55%) presented a risk of preterm birth. Despite tocolytic treatment, three (25%) patients at risk of preterm birth gave birth prematurely. The first of these patients presented febrile diarrhea. She gave birth at 33 weeks and 3 days of gestation, with no complications other than intrauterine growth retardation. The second patient presented febrile diarrhea and was carrying twins.

TABLE 2

Obstetric complications as a function of term and initial treatment

	Isolated uterine contractions N (%)	Risk of miscarriage N (%)	Risk of preterm birth N (%)	Mother-to-child transmission N (%)
As a function of term				
First trimester ($N = 2$)	0 (0)	0 (0)	NA	0 (0)
Second trimester ($N = 4$)	0 (0)	2 (50)	NA	0 (0)
Third trimester < 37 weeks ($N = 22$)	3 (14)	NA	12 (55)	0 (0)
Third trimester > 37 weeks ($N = 9$)	NA	NA	NA	3 (33)
As a function of initial treatment				
No treatment or ineffective treatment ($N = 6$)	1 (17)	0 (0)	0 (0)	3 (50)
Susceptible ($N = 20$)	2 (10)	1 (5)	5 (25)	0 (0)
Intermediate ($N = 7$)	0 (0)	0 (0)	5 (71)	0 (0)
Resistant ($N = 4$)	0 (0)	1 (25)	2 (50)	0 (0)

NA = not appropriate.

At 32 weeks and 4 days of gestation, the pregnancy was complicated by the death in utero of one of the twins and the birth, on the same day, of the second twin. The third patient underwent a cesarean section at 35 weeks and 2 days of gestation, due to a fetal heart rate anomaly in the context of diarrhea. All but one of the nine patients diagnosed at a term exceeding 37 weeks of gestation gave birth at the maternity unit. The remaining patient gave birth at home. On the third day postpartum, two of the neonates presented episodes of diarrhea with no signs of dehydration or associated fever. In both cases, the mother had febrile diarrhea at the time of delivery. Cultures of stools from the neonates demonstrated the presence of *S. flexneri* and *S. sonnei*. A stool culture was carried out for one of the mothers, but was negative. The clinical course after oral rehydration was favorable for the two neonates, with no need for antibiotic prescription. The third case of mother-to-child transmission was demonstrated by a gastric sample that was positive for *S. flexneri*. The sample was taken in the framework of a neonatal bacteriological evaluation. Neither the neonate nor the mother had clinical symptoms. No maternal stool culture was carried out.

A risk of late miscarriage or preterm birth occurred in 35% ($N = 6/17$) of patients treated with a drug to which the infecting strain was susceptible before 37 weeks of gestation. Patients not receiving appropriate treatment (i.e., no treatment [$N = 1$], empirical treatment with an antibiotic to which the strain concerned displayed intermediate susceptibility ($N = 5$) or resistance ($N = 4$), or treatment with an antibiotic inactive against *Shigella* (secnidazole, $N = 1$) presented a risk of late miscarriage and preterm birth in 73% of cases ($N = 8/11$). This difference was of borderline significance (Fisher's test; $P = 0.053$).

Microbiology. We obtained 36 isolates from stool cultures (34 maternal stool cultures and two neonatal stool cultures) and one from a neonatal gastric sample. *Shigella flexneri* accounted for 84% of the isolates obtained ($N = 31/37$) and *S. sonnei* accounted for 11% ($N = 4/37$). The species was not identified for two strains (5%). The susceptibility of the isolates to the antibiotics tested is summarized in Table 3. The isolates were resistant to penicillins (resistance rates of 80%

for amoxicillin, 59% for ampicillin, 70% for ticarcillin, 16% for amoxicillin/clavulanic acid, and 8% for cefalotin) and cotrimoxazole (62%). All the isolates were susceptible to third-generation cephalosporins and fluoroquinolones. All bacteriological samples other than stool cultures were negative for *Shigella* (blood cultures, cytobacteriological examinations of urine, vaginal samples, and placenta cultures).

DISCUSSION

In addition to the symptoms accompanying the episodes of diarrhea (abdominal pain and fever), 61% of our patients with a term of less than 37 weeks [$N = 17/28$] presented uterine contractions. Cervical changes were associated with uterine contractions in 82% of cases ($N = 14/17$), defining a risk of late miscarriage (two cases) or of preterm birth (12 cases). Overall, 25% ($N = 3/12$) of the women presenting a risk of preterm birth gave birth prematurely, despite tocolytic treatment (with the death in utero of one fetus in a twin pregnancy). Three cases of mother-to-child transmission were identified.

This study has several limitations, the most important of which is the retrospective method used. Episodes of shigellosis do not necessarily require hospital consultation and were therefore probably largely underestimated. This study is therefore unlikely to be representative of all cases of shigellosis occurring in pregnant women during the study period. Nevertheless, it concerns the largest series of cases of shigellosis during pregnancy ever reported.

Few cases of shigellosis occurring during pregnancy have been described in previous studies. Markham and others provided the first description of a case of maternal septicemia associated with an intrauterine infection. The patient concerned was from Ghana and had stage 3 human immunodeficiency virus (HIV) infection. It was her first pregnancy and shigellosis occurred at 34 weeks and 2 days of gestation. She presented nausea, vomiting, and weight loss. Signs of fetal distress (a fetal heart rate anomaly) led to an emergency cesarean section. A maternal blood culture was positive for *S. sonnei*. The symptoms present at birth (alternation of irritability and lethargy) and the composition of the cerebrospinal fluid (hypoglycorrhachia, hyperleukocytosis, hyperproteinorachia) were consistent with neonatal meningitis, but a culture of cerebrospinal fluid was negative. The neonate presented no gastrointestinal signs.³ Armor and others described a case of chorioamnionitis at term associated with neonatal bacteremia and pneumonia (with negative maternal blood cultures).⁴ Rebarber and others described a case of shigellosis complicating premature membrane rupture and leading to congenital infection and preterm birth at 25 weeks and 6 days of gestation. The patient had bloody mucus-containing diarrhea, abdominal cramps, and nausea associated with premature membrane rupture. Signs of fetal distress (meconial liquid and a fetal heart rate anomaly) led to an emergency cesarean section. Cultures of maternal and fetal feces and of the placenta were positive for *S. sonnei*. Pathological examination of the placenta suggested chorioamnionitis. Culture of a sample from the upper end of the vagina was positive, whereas that of a sample from the lower end of the vagina was negative. The congenital transmission of the infection was considered to be hematogenous, despite the negative results obtained for maternal blood cultures.⁵ Ruderman and others described a case of shigellosis due to *S. sonnei* associated with asymptomatic neonatal bacteremia, during the immediate

TABLE 3
Proportion of isolates resistant to the antibiotics tested

Antibiotics tested	No. of resistant isolates	No. of isolates tested	Proportion of isolates resistant (%)
Amoxicillin/clavulanic acid	6	37	16
Amoxicillin	16	20	80
Ampicillin	10	17	59
Ticarcillin	26	37	70
Piperacillin/tazobactam	0	37	0
Cefalotin	3	37	8
Cefotaxime	0	37	0
Ceftazidime	0	37	0
Cefoxitin	0	37	0
Imipenem	0	37	0
Tobramycin	0	37	0
Amikacin	0	37	0
Netilmycin	0	28	0
Gentamicin	0	37	0
Nalidixic acid	1	37	3
Ofloxacin	0	30	0
Ciprofloxacin	0	37	0
Cotrimoxazole	23	37	62

postpartum period. Maternal stool cultures were positive, whereas maternal blood cultures were negative.⁶ Finally, a study based on samples of lower segments of the uterus dissected out during cesarean section showed that a dose of 10^5 *Shigella*/mL was sufficient to induce a significant increase in uterine contractile activity.⁷

Neonatal shigellosis seems to be associated with higher rates of morbidity and mortality than shigellosis in older children.⁸ Cases of necrotizing enterocolitis, septicemia, pneumonia, convulsions, meningitis, splenic necrosis, and pericardiac microabscesses have been described.^{4-6,9,10} The published cases concern principally the species *S. sonnei*^{3,5,6,10} and *Shigella boydii*.⁹

This study is, to our knowledge, the first to provide a clinical description of an association between episodes of shigellosis during pregnancy and the occurrence of uterine contractions and cervical modifications. The consequences of shigellosis may therefore include miscarriage or preterm birth. Prematurity is a major risk factor for perinatal morbidity and mortality. The uterine contractions may be triggered by *Shigella* or may be a consequence of the infectious state itself (fever, peritoneal irritation, abdominal spasms). Certain serotypes of *Shigella* secrete toxins that may trigger uterine contractions (Shiga toxin, secreted by *Shigella dysenteriae* type 1; SHET1 toxin, secreted by some *Shigella* 2a strains; and SHET2 toxin, secreted by several *Shigella* strains of different serotypes and by enteroinvasive *Escherichia coli*).¹¹

Mother-to-child transmission may be congenital, following maternal bacteremia, as suggested by Rebarber and others in their study, in which *Shigella* was absent from the lower end of the vagina and present in the membranes, and by Markham and others, who observed the secondary neonatal transmission of septicemia in a patient with stage 3 HIV infection. The infection may also be transmitted during delivery, during passage through the genital apparatus or after the birth, through direct contact (hygiene and hand washing are therefore important for prevention). The symptoms then appear during the first few days of life. In this study, two cases of mother-to-child transmission were found to have resulted from maternal infection during the perinatal period. Indeed, at the time of the delivery, the two mothers concerned presented diarrhea and a febrile syndrome. Neonatal transmission seems to have occurred at the time of delivery, with neonatal symptoms appearing during the first 3 days after birth. The third case of mother-to-child transmission seems to have resulted from chronic maternal carriage of *Shigella*. The mother had no symptoms at the time of delivery and fetal infection was demonstrated by the presence of *Shigella* in the gastric sample collected for the neonatal examination. The neonate had no symptoms.

Similar complications are observed in cases of typhoid fever during pregnancy.¹² Like *Shigella*, *Salmonella typhi* belongs to the Enterobacteriaceae. It causes chorioamnionitis secondary to septicemia of digestive origin. The potential complications of infection with this bacterium are miscarriage, fetal death in utero, neonatal infection, and diverse maternal complications.

Rehydration is the cornerstone of diarrhea treatment. However, antibiotic treatment is also required in cases of moderate and severe shigellosis, as it can decrease complications and disease transmission. In this study, the initiation of appropriate antibiotic treatment seemed to prevent the risk of preterm birth and late miscarriage (35% versus 75% for women not

given appropriate treatment, $P = 0.053$). The three cases of mother-to-child transmission occurred in untreated patients in whom the infection was diagnosed after the fact. The antibiotics recommended by the World Health Organization (ciprofloxacin as a first-line treatment, ceftriaxone or azithromycin as a second-line treatment) are suitable for use in pregnant women.¹³ In French Guiana, empirical treatment could be based on ceftriaxone or ciprofloxacin because the strains isolated locally are susceptible to these antibiotics. Particular attention should be paid to episodes of shigellosis in pregnant women, to prevent obstetric and neonatal complications.

CONCLUSION

Episodes of shigellosis during pregnancy seem to trigger uterine contractions and cervical modifications in some cases, potentially leading to late miscarriage or preterm birth. Prematurity is a major risk factor for perinatal morbidity and mortality. The uterine contractions may be caused directly by *Shigella* or may be a consequence of the infectious state. The obstetric and neonatal complications are potentially severe. Neonatal transmission may be congenital, following maternal bacteremia. It may also occur during delivery, during passage through the genital apparatus or after the birth, by direct contact (hygiene and hand washing are therefore important for prevention).

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REFERENCES

1. von Seidlein L, Kim DR, Ali M, Lee H, Wang X, Thiem VD, Canh do G, Chaicumpa W, Agtini MD, Hossain A, Bhutta ZA, Mason C, Sethabutr O, Talukder K, Nair GB, Deen JL, Kotloff K, Clemens J, 2006. A multicentre study of *Shigella* diarrhoea in six Asian countries: disease burden, clinical manifestations, and microbiology. *PLoS Med* 3: e353.
2. INSEE, 2012. *Population selon le sexe et l'âge au 1er janvier*. Available at: <http://www.insee.fr>.
3. Markham KB, Backes C, Samuels P, 2012. Bacteremia and intra-uterine infection with *Shigella sonnei* in a pregnant woman with AIDS. *Arch Gynecol Obstet* 286: 799–801.
4. Armor SA, 1990. Periparturitional shigellosis. *Nebr Med J* 75: 239–241.
5. Rebarber A, Star Hampton B, Lewis V, Bender S, 2002. Shigellosis complicating preterm premature rupture of membranes resulting in congenital infection and preterm delivery. *Obstet Gynecol* 100 (Suppl 2): 1063–1065.
6. Ruderman JW, Stoller KP, Pomerance JJ, 1986. Bloodstream invasion with *Shigella sonnei* in an asymptomatic newborn infant. *Pediatr Infect Dis* 5: 379–380.
7. Lechner W, Rosboth D, Fille M, Dierich M, Bergant A, Windbichler G, Kirchebner P, Sölder E, 1998. Induction of uterine contractions by shigellae. *Z Geburtshilfe Neonatol* 202: 38–39.

8. Huskins WC, Griffiths JK, Faruque ASG, Bennish ML, 1994. Shigellosis in neonates and young infants. *J Pediatr* 125: 14–22.
9. Sawardekar KP, 2005. Shigellosis caused by *Shigella boydii* in a preterm neonate, masquerading as necrotizing enterocolitis. *Pediatr Infect Dis J* 24: 184–185.
10. Moore EEM, 1974. *Shigella sonnei* septicaemia in a neonate. *BMJ* 1: 22.
11. Germani Y, Sansonetti P, 2008. *Shigellose et infections à Escherichia coli entéro-invasifs*. Elsevier Masson, 1–17.
12. Carles G, Montoya Y, Seve B, Rakotofananina T, Largeaud M, Mignot V, 2002. Typhoid fever and pregnancy. *J Gynecol Obstet Biol Reprod (Paris)* 31: 495–499.
13. World Health Organization, 2005. *Guidelines for the control of shigellosis, including epidemics due to Shigella dysenteriae*. Geneva, Switzerland: World Health Organization.