

Short-Acting Sulfonamides Near Term and Neonatal Jaundice

Pia Klarskov, MD, Jon Trærup Andersen, MD, PhD, Espen Jimenez-Solem, MD, Christian Torp-Pedersen, MD, DMSc, and Henrik E. Poulsen, MD, DMSc

OBJECTIVE: To investigate the association between maternal use of sulfamethizole near term and the risk of neonatal jaundice.

METHODS: We conducted a nationwide population-based retrospective cohort study using Danish registers. All Danish women giving birth between 1995 and 2007 were included from the Danish Fertility Database. Women redeeming a prescription for sulfamethizole up to 4 weeks before giving birth were identified from the National Prescription Register. The primary outcome was the number of neonates diagnosed with jaundice between birth and age 28 days identified in the National Hospital Register. Risk of neonatal jaundice was calculated as odds ratios (ORs) with linear logistic regression with and without adjustment for confounders.

RESULTS: We identified 841,900 births. Of 1,823 (0.2%) neonates exposed to sulfamethizole up to 4 weeks before birth, 197 (10.8%) developed neonatal jaundice. The OR of developing neonatal jaundice after exposure to sulfamethizole was 2.35 (95% confidence interval [CI] 2.02–2.72). Adjustment for maternal age, education, household income, parity, and period of conception left OR unchanged at 2.29 (95% CI 1.97–2.67). After further adjustment for gestational age, the risk associated with sulfamethizole was rendered insignificant (OR 1.03, 95%

CI 0.86–1.22). Narrowing exposure time to the last week before birth did not change the estimates. Broken into gestational age groups, the rate of neonates with jaundice after exposure was similar to the rate of unexposed neonates with jaundice.

CONCLUSIONS: We found no association between redeeming a prescription of sulfamethizole near term and increased risk of neonatal jaundice. We showed that the presumed association is the result of preterm birth, which can be caused by maternal urinary tract infection.

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LEVEL OF EVIDENCE: II

Sulfamethizole is an inexpensive and effective short-acting sulfonamide, in Denmark primarily used in antibacterial treatment of urinary tract infections. Urinary tract infections occur in up to 20% of pregnancies and are, if left untreated, associated with a higher frequency of unwanted pregnancy outcomes including preterm delivery.¹

Sulfamethizole carries a theoretical risk of causing neonatal jaundice, icterus, and kernicterus if prescribed to a pregnant woman late in pregnancy or to a lactating woman with a premature or unhealthy neonate.^{2–4} There is a high rate of turnover of red blood cells in the neonate and neonates have a limited ability to conjugate bilirubin, leading to a relatively increased level of unconjugated bilirubin in normal neonates. It is known that sulfonamides compete with unconjugated bilirubin for plasma albumin binding, further increasing levels of unbound unconjugated bilirubin.⁵ In the neonate, this bilirubin can cross the newborn's immature blood–brain barrier resulting in kernicterus. During pregnancy, the sulfonamides cross the placenta readily, achieving fetal equilibrium at 70–90% of maternal levels within 2–3 hours.²

Toxicity of sulfonamides administered to neonates is well established, but the risk of developing neonatal jaundice after the mother's exposure to short-acting

From the Laboratory of Clinical Pharmacology Q7642, Rigshospitalet, the Department of Clinical Pharmacology, Bispebjerg Hospital, the Faculty of Health Sciences, University of Copenhagen, and the Department of Cardiology, Gentofte Hospital, Copenhagen, Denmark.

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Corresponding author: Pia Klarskov, MD, Laboratory of Clinical Pharmacology Q7642, Rigshospitalet, Tagensvej 20, DK-2200 Copenhagen, Denmark; e-mail: pia.klarskov@mail.dk.

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sulfonamides is based on theoretical considerations. The risk has been assessed in a regional Danish study published in 2003, which questioned the association, but the study was too small to be conclusive.⁶

We therefore examined the association between redeeming a prescription for the short-acting sulfonamide sulfamethizole in the last 4 weeks of pregnancy and neonatal jaundice in a nationwide retrospective cohort study including more than 800,000 pregnancies.

MATERIALS AND METHODS

The study period was from January 1, 1995, to December 31, 2007. We used information from the Danish Fertility Database,⁷ the Danish National Prescription Register,⁸ the Danish National Patient Register,⁹ and Statistics Denmark.¹⁰ Data in these registers were linked through the unique 10-digit personal identification number assigned to all Danish citizens at birth or immigration.

We used the Danish Fertility Database to identify all pregnancies in the study period including information on the mother's previous births, neonate's gestational age, and death status. More than 99.5% of births in Denmark since 1978 are registered in the Danish Fertility Database.⁷ The register was validated by comparing its variables with records registered by midwives during pregnancy. Births resulting in stillbirth ($n=3,344$) and records with coding errors or missing information ($n=12,861$) were excluded, resulting in a cohort of 841,900 births. After excluding these records, the final cohort consisted of 98% of all births in the study period. Time of conception in Denmark is based on ultrasonographic estimates¹¹ or the date of the last menstrual period. Maternal highest obtained education and annual household income were collected from Statistics Denmark.

The Danish National Prescription Registry contains information on all prescription drugs dispensed at all Danish pharmacies.⁸ The register includes drugs identified by Anatomical Therapeutic Chemical classification codes and dispensing date. Medications dispensed at hospitals are not included in the register. Pharmacies are required by law to register prescriptions and this activity is coupled with reimbursement of expenses from the state, which ensures highly accurate prescription data. Completeness has previously been estimated to be 97.5% by comparing register records on strong analgesics with records from the Surveillance System on Strong Analgesics.¹²

Exposure was defined as redemption of a prescription for sulfamethizole during the last 4 weeks of pregnancy, which was identified according to the Anatomical Therapeutic Chemical code (J01EB02).

To investigate exposure closer to term, the exposure time period was reduced further to the last week before birth.

The Danish National Patient Register holds all admission and outpatient records in Denmark since 1978 and includes information on date of admission and discharge and discharge diagnosis.⁹ It holds more than 99% of discharge records from all Danish hospitals.¹³

Outcomes were defined as neonate diagnosed with jaundice (International Classification of Diseases, 10th Revision codes DP58, DP59, and DR17) between birth and age 28 days. Only hospital diagnoses were included, because diagnoses from general practitioners were not available.

Women were categorized into five groups according to their age at parturition: younger than 20 years, 20–24 years, 25–29 years, 30–34 years, and older than 34 years (0% missing values). Educational level was divided into three groups: short, medium, and long according to the highest obtained level of education at the end of the birth year (6% missing values).

Table 1. Basic Characteristics of Mothers

	Sulfamethizol ($n=1,823$; 0.2%)	No Sulfamethizol ($n=840,077$; 99.8%)	<i>P</i>
Age (y)			
Younger than 20	92 (5.1)	24,185 (2.9)	<.001
21–25	392 (21.5)	137,395 (16.4)	
26–30	661 (36.3)	325,682 (38.8)	
31–35	488 (26.8)	258,079 (30.7)	
Older than 35	190 (10.4)	94,736 (11.3)	
Educational level			
High school or less	692 (38.0)	271,306 (32.3)	<.001
Technical education	578 (31.7)	266,894 (31.8)	
Postsecondary	428 (23.5)	251,206 (29.9)	
Household income*			
Less than \$62,192	536 (29.4)	193,931 (23.1)	<.001
\$62,192–89,140	442 (24.3)	202,391 (24.1)	
\$89,141–126,344	425 (23.3)	217,149 (25.9)	
More than \$126,344	419 (23.0)	225,456 (26.8)	
Year of conception			
1995–1998	548 (30.1)	311,638 (37.1)	<.001
1999–2003	646 (35.4)	323,279 (38.5)	
2004–2007	629 (34.5)	205,160 (24.4)	
Parity			
1	821 (45.0)	363,983 (43.3)	.178
2	653 (35.8)	313,648 (37.3)	
3	241 (13.2)	119,767 (14.3)	
More than 3	108 (5.9)	42,666 (5.1)	

Data are n (%) unless otherwise specified.

* 2008 values.



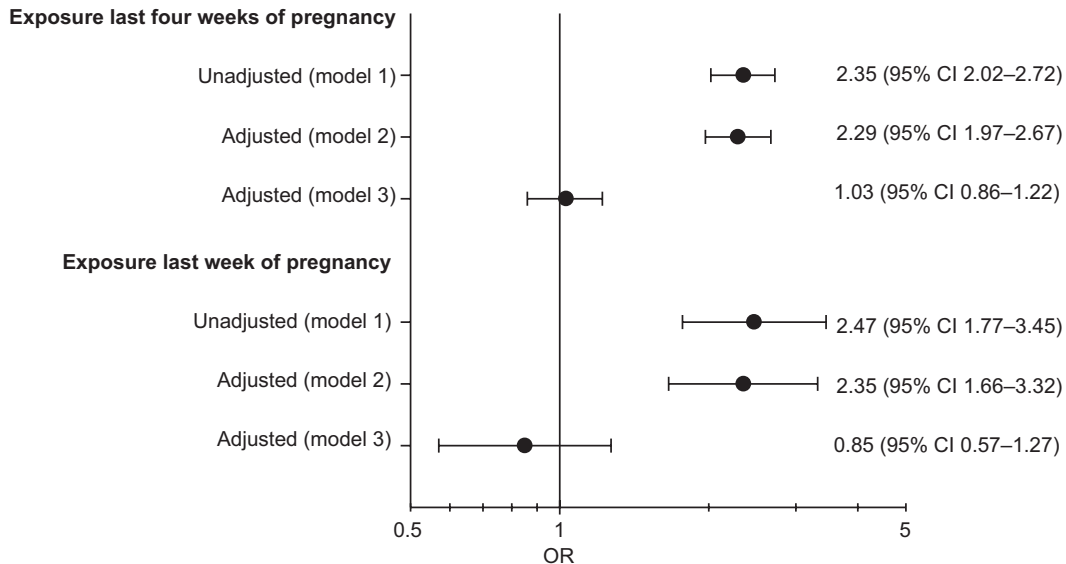


Fig. 1. Odds ratio (OR) of neonatal jaundice after exposure to sulfamethizole near term. Model 2: adjusted for age, education, household income, parity and year of conception. Model 3: adjusted for age, education, household income, parity, year of conception, and gestational age. CI, confidence interval.

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Household income was divided into quartiles according to annual gross income during the birth year (0.1% missing values). Parity was defined as number of births, including previous stillbirths, and divided into four classes corresponding to the number of births: one, two, three, and more than three births (0% missing values). Year of conception was categorized into three groups: 1995–1998, 1999–2003, and 2004–2007 (0% missing values). Gestational age was categorized into five groups: less than 28 weeks, 28–31 weeks, 32–36 weeks, 37–39 weeks, and greater than 39 weeks.

Three logistic regression models were used on dichotomous outcomes to estimate the odds ratios of jaundice. Model one was unadjusted; model two was adjusted for age, education, household income, parity, and year of conception; and model three was in addition adjusted for gestational age.

Rate of jaundice was compared between groups of newborns exposed to sulfamethizole and unexposed newborns. Frequencies and percentages were used to present baseline characteristics. χ^2 tests were used to assess differences for categorical variables. Odds ratios (ORs) are presented with 95% confidence intervals (CIs). Statistical significance was defined as $P < .05$. All statistical tests were two-sided. Data management and all statistical analyses were performed using SAS 9.2.

To ensure that no individuals could be identified, all personal information held in the registers was encrypted and analyzed on computers held by Statistics

Denmark. The present study has been approved by The Danish Data Protection Agency (No. 2008-41-2517). Retrospective register studies do not require ethical permission in Denmark.

RESULTS

We identified 841,900 pregnancies. Mothers exposed to sulfamethizole near term tended to be younger, have a shorter education, and a lower household income compared with those unexposed (Table 1).

Neonatal jaundice within 28 days after birth was registered for 41,498 (4.9%) newborns in the study

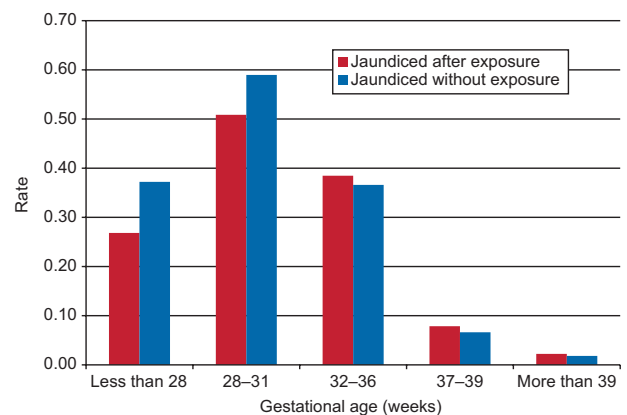


Fig. 2. Rate of jaundiced neonates with or without exposure to sulfamethizole near term.

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Table 2. Rate of Neonatal Jaundice by Gestational Age in Exposed and Unexposed Groups

Neonatal Outcome	Gestational Age (wk)			
	Less Than 28		28–31	
	Sulfamethizol	No Sulfamethizol	Sulfamethizol	No Sulfamethizol
Jaundice	11	737	30	3,004
No jaundice	30	1,243	29	2,090
χ^2 test	$P=.16$		$P=.21$	

Data are n unless otherwise specified.

cohort. Sulfamethizole exposure during the last 4 weeks of pregnancy was registered for 1,823 newborns of which 197 (10.8%) developed neonatal jaundice. Of the 840,077 unexposed, 41,301 (4.9%) were registered with neonatal jaundice. When restricting the exposure time to the last week of pregnancy, we found 344 neonates exposed to sulfamethizole of which 39 (11.3%) developed jaundice.

The risk of developing neonatal jaundice (Fig. 1) after being exposed to sulfamethizole in the last 4 weeks of pregnancy (model 1) was OR 2.35 (95% CI 2.02–2.72). Adjustment for mother's age, education, household income, period of conception, and parity (model 2) gave an OR of 2.29 (95% CI 1.97–2.67). Further adjustment for gestational age (model 3) resulted in an OR of 1.03 (95% CI 0.86–1.22).

Defining exposure as the last week of pregnancy gave similar results (Fig. 1). Broken into gestational age groups, the rate of jaundiced neonates in the exposed group is similar to the rate of jaundiced neonates in the unexposed group (Fig. 2; Table 2).

Short-acting sulfonamides are believed to cause kernicterus when used near term.² In our cohort, only 18 developed kernicterus, of which none had been exposed to sulfamethizole during the last 4 weeks of pregnancy.

DISCUSSION

The present study of 841,900 pregnancies shows no association between intrauterine exposure to sulfamethizole during the last 4 weeks of pregnancy and development of neonatal jaundice. We cannot make any conclusions regarding kernicterus. In the unadjusted analysis, we found a doubling in the risk of having jaundice in neonates born by mothers exposed to sulfamethizole. However, when we adjusted for gestational age, the OR was 1.

Sulfamethizole is inexpensive and has fewer adverse effects than other drugs used for treating urinary tract infection.¹⁴ The standard dosage in Denmark for treating urinary tract infections with sulfamethizole during pregnancy is 1 g twice daily for

6 days. If our results are confirmed by other large-scale studies, the drug can be acquitted for the risk of neonatal jaundice and kernicterus and available for treatment of urinary tract infection also near term.

Our study is nationwide, covering all pregnancies in the study period and thereby avoiding selection bias. The Danish Fertility Database holds more than 99.9% of all births in Denmark.¹⁵ Pharmacies are required by law to register prescriptions because this is coupled to the reimbursement of drug expenses from the Danish government. This ensures high accuracy of prescription data with a completeness of up to 99%.¹⁶

Limitations of our study include the lack of information about medication administered to pregnant women during hospitalization, lack of information on drug dosage, treatment indication, compliance, and possible flawed registration of diagnoses. Furthermore, our registers do not contain information on bilirubin levels, which could determine a possible dose–effect relationship. Package size and strength of redeemed prescriptions are available, but information on treatment dosage is unavailable. Treatment indication is not registered in the Danish National Prescription Register, but the main and possibly sole indication for prescribing sulfamethizole in Denmark is urinary tract infection. Our study results rely on compliance. Lack of compliance would result in a possible flawed estimation of the association between intrauterine exposure to sulfamethizole and neonatal jaundice and push the estimates toward unity. However, a Dutch study estimated that pregnant women redeeming a prescription were very likely to take their medication.¹⁷ Urinary tract infections are potentially harmful for the fetus and could lead to early delivery. Therefore, we find it likely that compliance is high. Diagnoses of neonatal jaundice are not available from general practitioners, which limits our study to diagnoses given during hospitalization.

A study published in 2003 by Ratanajamit et al investigated the association between exposure to sulfamethizole near term and neonatal jaundice in the Danish county of North Jutland⁶ including a cohort of 63,659 pregnancies. They found no



Gestational Age (wk)					
32–36		37–39		40 or More	
Sulfamethizol	No Sulfamethizol	Sulfamethizol	No Sulfamethizol	Sulfamethizol	No Sulfamethizol
80	12,286	59	14,777	17	10,497
128	21,282	692	208,453	747	565,708
<i>P</i> =.58		<i>P</i> =.19		<i>P</i> =.42	

association between redeeming a prescription for sulfamethizole and neonatal jaundice whether looking at exposure up to 30 days before delivery (crude OR 3.89, 95% CI 1.52–9.94, adjusted OR [including gestational age] 1.14, 95% CI 0.38–3.46) or exposure up to 14 days before delivery (crude OR 1.99, 95% CI 0.92–4.28, adjusted OR 0.94, 95% CI 0.39–2.26). In contrast to Ratanajamit et al's study, our study population is nationwide, giving us 13 times as many cases. Furthermore, we analyzed exposure closer to delivery (7 days), thereby increasing the probability of exposure at birth. The results of both studies are similar, and because our study is considerably larger, it further corroborates the findings of the Ratanajamit et al.

Published literature states that sulfonamides can cause severe jaundice and kernicterus and that sulfonamides, including short-acting sulfonamides such as sulfamethizole, should be avoided in late pregnancy.^{2–4} This precaution is based on earlier studies (1941–1971) of different sulfonamides.^{18–21} However, none of these were short-acting sulfonamides. A later study from 1980 on the intermediate-acting sulfonamide sulfadiazine showed no increase in hyperbilirubinemia or kernicterus in the 94 newborns exposed near term compared with other neonates in the same nursery.²² The precautions regarding short-acting sulfonamides seem, therefore, to be theoretical and not scientifically or empirically based. There are several types of sulfonamides, but we have found no literature describing differences in the drugs' ability to displace bilirubin. Therefore, we believe that our results are applicable to the remaining sulfonamides.

Sulfamethizole has a plasma half-life of 2 hours, indicating that exposure must be very close to birth to affect the newborn, because unbound bilirubin is readily cleared through the placenta until birth. Reducing the exposure time period to the last week of pregnancy increases the probability that the newborn has sulfamethizole in plasma at the time of birth. Although it reduces the number of exposed newborns to 39, it shows results similar to exposure during the last 4 weeks of pregnancy.

Our study of 841,900 pregnancies indicates no association between exposure to sulfamethizole near term and neonatal jaundice. Instead it is more likely that maternal urinary tract infection may cause prematurity and thereby increased risk of neonatal jaundice. Sulfamethizole is inexpensive and effective, and it might therefore be time to disregard old hypothetical views on sulfonamides.

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