

Smallpox during Pregnancy and Maternal Outcomes

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A historical study evaluated maternal outcomes in pregnancy complicated by smallpox. The overall case fatality was estimated to be 34.3% (95% confidence interval [CI] 31.4–37.1), and the proportion of miscarriage or premature birth was estimated to be 39.9% (95% CI 36.5–43.2). Vaccination before pregnancy reduced the risk for death.

Pregnant women are at special risk for complications of smallpox vaccination (1); therefore, vaccination is not recommended for pregnant women in the absence of a reemergence of smallpox (2). Smallpox in pregnancy is believed to be more severe than in nonpregnant women or adult men (3), but this consensus is based on a limited number of studies conducted during the mid-20th century (4–6). This article examines the outcomes of pregnancy complicated by smallpox in historical records from the 19th and 20th centuries.

The Study

Since most large outbreaks were documented before the mid-20th century, I collected and reviewed the literature dating back to the 19th century. Technical details of the literature review are provided in online Appendix 1 (available at http://www.cdc.gov/ncidod/EID/vol12no07/05-1531_app1.htm). All selected publications were retrospective studies based on epidemiologic observations of outbreaks that reported case fatalities, miscarriages, or premature births. Because vaccination or advances in obstetrics over time could bias these outcomes, these factors were abstracted from each publication and considered separately, when possible. Outcomes were then stratified by gestation period at onset of smallpox (by trimester), clinical classification of smallpox, and vaccination history. Case fatalities were compared between pregnant and nonpregnant patients. Except in Rao's work in Madras (4), miscarriage and premature birth were not separated, so they are described together.

Nineteen outbreaks were identified from historical records (4,7–20), and of these, 16 allowed estimates to be made of case fatality, and 15 allowed estimates of the pro-

portion of miscarriage or premature birth. Of 1,074 pregnant patients, 368 died; and of 830 pregnant patients, 331 miscarried or gave birth prematurely (Figure). Since these articles are from many years ago, the proportion of cases that were undetected or unreported cannot be determined nor can the length of time since vaccination in persons who were vaccinated. Descriptions of excluded literature are given in online Appendix 1; individual case records were provided in 3 outbreaks and are included in online Appendix 2 (available at http://www.cdc.gov/ncidod/EID/vol12no07/05-1531_app2.htm).

Figure, panel A, shows the distribution of estimated case fatalities for each outbreak with the corresponding 95% confidence intervals (CIs). Case fatalities varied widely among outbreaks. The earliest outbreak in 1830 (before compulsory vaccination) yielded the highest estimate (81.5%), while the 1913 outbreak in Australia had the lowest (4.3%). The overall crude case fatality was estimated to be 34.3% (95% CI 31.4–37.1). Case fatality, stratified by gestational age at onset of smallpox, is presented in Table 1; only 4 studies enabled stratification by gestational age. Case fatality was highest during the third trimester, except in Queirel's study, which included few cases (18). Case fatality, stratified by the clinical classification of smallpox, is shown in online Appendix 2. All patients with hemorrhagic cases died, but all patients without a rash (variola sine eruptione, VSE) survived.

Case fatalities among pregnant and nonpregnant patients are compared in Appendix 2. Case fatality was not

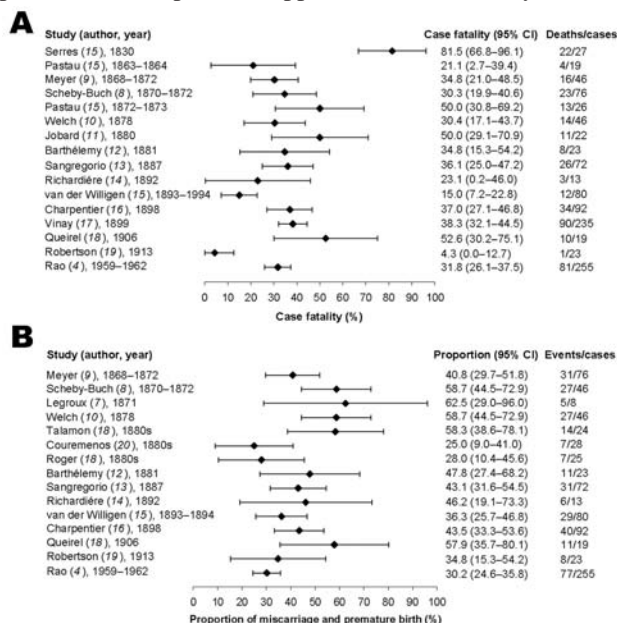


Figure. Maternal outcomes in pregnancies complicated by smallpox from data from 19th- and early 20th-century outbreaks. A) Case fatalities and B) proportions of miscarriage or premature birth are shown. Miscarriage and premature birth before maternal death are included.

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Table 1. Case fatality among pregnant women with smallpox by gestational age, according to data from 19th- and early 20th-century outbreaks*

Reference	Gestational age ≤ 3 mo		Gestational age 4–6 mo		Gestational age 7–9 mo	
	D/C	CF (95% CI)	D/C	CF (95% CI)	D/C	CF (95% CI)
Meyer (9), 1868–1872	3/33	9.0 (0.0–18.9)	11/33	33.3 (17.2–49.4)	8/10	80.0 (55.2–100.0)
Welch (10), 1878	4/12	33.3 (6.7–60.0)	4/22	18.2 (2.1–34.3)	6/12	50.0 (21.7–78.3)
Queirel (18), 1906	2/4	50.0 (1.0–99.0)	7/10	14.5 (4.6–98.4)	1/5	17.9 (0.0–55.1)
Rao (5), 1959–1962	7/21	33.3 (13.2–53.5)	16/65	24.6 (14.1–35.1)	34/94	36.2 (26.5–45.9)
Total	16/70	22.9 (2.3–43.4)	38/130	29.2 (14.8–43.7)	49/121	40.5 (26.8–54.2)

*D/C, smallpox deaths/cases; CF, case fatality; CI, confidence interval.

significantly higher in pregnant patients in the Rotterdam outbreak ($p = 0.33$), where many VSE cases apparently occurred. The risks for a fatal outcome among pregnant patients in Berlin and Madras were 2.5 \times and 4.2 \times higher than among nonpregnant patients ($p < 0.01$ for each). I also compared vaccinated and unvaccinated pregnant patients, showing that the risk for death was significantly higher among unvaccinated women in these 3 outbreaks (7/7 vs. 7/39, $p < 0.01$; 2/2 vs. 10/78, $p = 0.02$; and 9/12 vs. 17/82, $p < 0.01$, respectively).

Crude proportions of miscarriage and premature birth, with 95% CI, are given in the Figure, panel B. The overall crude proportion of miscarriage or premature birth is estimated to be 39.9% (95% CI 36.5–43.2). Five outbreaks allowed stratification by gestational age at onset of smallpox (Table 2). The overall proportion of premature birth was highest during the last trimester of pregnancy, but no clear pattern was seen with regard to the frequency of miscarriage or premature birth. The proportion of miscarriage and premature birth, stratified by severity of smallpox, is shown in online Appendix 2. All hemorrhagic cases resulted in either miscarriage or premature birth before the mother's death. Even mild cases, those classified as discrete or VSE, tended to result in miscarriage or premature birth. Only the 1878 outbreak in Philadelphia (10) allowed a comparison between vaccinated and unvaccinated pregnant patients. Twenty-two of 39 vaccinated and 5 of 7 unvaccinated patients miscarried or delivered prematurely ($p = 0.68$).

These outcomes could only be compared by history of miscarriage in the 1913 outbreak in Australia (19). Two of 3 patients with no history and 6 of 20 with a history of miscarriage had a miscarriage or premature birth, but this dif-

ference was not significant ($p = 0.27$, odds ratio 4.7, 95% CI 0.4–61.8). Comparison by previous experience of normal delivery (primipara or multipara) could only be performed with the data from Rotterdam from 1893 and 1894 (15). Ten of 21 primipara patients and 18 of 53 multipara patients had a miscarriage or premature birth ($p = 0.30$), which suggests that delivery history did not greatly affect the outcome of pregnancy complicated by smallpox.

Conclusions

Since outbreaks have been limited since the mid-20th century by the successful smallpox eradication program, historical records are a useful tool to document common patterns of maternal outcomes in pregnancy complicated by smallpox. Such analysis may be limited by unknown numbers of missed or unreported cases or imperfect vaccination histories. My estimates of the overall crude case fatality and proportion of miscarriage or premature birth were high. This study and Rao's (4) improve our understanding of smallpox in pregnancy, highlighting 3 points. First, case fatality is highest during the last trimester of gestation, but miscarriage and premature birth do not vary by trimester. Physiologic changes in the third trimester could partly explain the higher case fatality (21). Second, even mild cases were at high risk of causing miscarriage or premature birth. Third, miscarriage and premature birth were not significantly associated with vaccination history or previous miscarriage or delivery. That is, vaccination may not prevent miscarriage and premature birth.

Although prior vaccination offers less protection to pregnant women than others (22), this study shows that vaccination might offer at least partial protection. Case fatality in the event of a bioterrorist attack could be

Table 2. Miscarriage or premature birth among pregnant women with smallpox by gestational age, according to data from 19th- and early 20th-century outbreaks*

Reference	Gestational age ≤ 3 mo		Gestational age 4–6 mo		Gestational age 7–9 mo	
	L/C	PL (95% CI)	L/C	PL (95% CI)	L/C	PL (95% CI)
Meyer (9), 1868–1872	7/33	21.2 (7.3–35.1)	16/33	48.5 (31.5–65.4)	8/10	80.0 (55.3–100.0)
Welch (10), 1878	8/12	66.7 (40.1–93.2)	9/22	40.9 (20.5–61.3)	10/12	83.3 (62.4–100.0)
Queirel (18), 1906	3/4	75.0 (32.8–100.0)	8/10	80.0 (55.3–100.0)	0/5	0 (NC)
Robertson (19), 1913	1/2	50.0 (0.0–100.0)	6/9	66.7 (36.0–97.3)	1/12	8.3 (0.0–23.9)
Rao (5), 1959–1962	10/21	47.6 (26.4–68.9)	16/65	24.6 (14.2–35.0)	41/94	43.6 (33.6–53.6)
Total	29/72	40.3 (29.0–51.5)	55/139	39.6 (31.5–47.7)	60/133	45.1 (36.7–53.5)

*L/C, miscarriage or premature birth/cases; PL, proportion of miscarriage and premature birth; CI, confidence interval; NC, not calculable.

lowered with vaccination before pregnancy and should be considered if the risk for such an attack is high.

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