MOTHERISK *UPDATE*

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Risk of varicella infection during late pregnancy

ABSTRACT

QUESTION I have a patient who contracted varicella at 26 weeks' gestation. She is very concerned and would consider termination if it were earlier in the pregnancy. What are the current predictions of risk for her fetus?

ANSWER Based on review of all available studies, we could not detect a single case of congenital varicella syndrome in the third trimester of pregnancy (0/208), as compared with 5/645 (0.78%) in the first and 9/592 (1.52%) in the second trimester (P <.01 third vs first and second). You can reassure your patient.

RÉSUMÉ

QUESTION L'une de mes patientes a contracté la varicelle à sa 26e semaine de gestation. Elle s'inquiète beaucoup et envisagerait un avortement si la grossesse n'était pas si avancée. Quelles sont les prédictions actuelles de risque pour son fœtus?

RÉPONSE En nous fondant sur toutes les études à notre disposition, nous n'avons pas pu cerner un seul cas du syndrome de la varicelle congénitale durant le troisième trimestre de la grossesse (0/208), par rapport à 5/645 (0,78%) durant le premier trimestre et 9/592 (1,52%) durant le deuxième trimestre (P< ,01 au troisième par rapport au premier et au deuxième). Vous pouvez rassurer votre patiente.

The varicella virus is teratogenic in humans. It results in serious and debilitating symptoms that include limb-shortening defects and eye and brain malformations.[1] Usually, seronegative women contract the virus from young children at home or at work (eg, teachers and caretakers). Typical of many rare syndromes, the morphologic pathology of congenital varicella syndrome (CVS) has been described in case reports.[1] Only during the last decade have several large epidemiologic studies directly investigated the incidence of CVS among exposed fetuses.

We systematically reviewed all cohort studies to quantify the incidence of CVS in order to counsel pregnant women exposed to varicella. We searched MEDLINE, EMBASE, and textbooks on infection during pregnancy and lactation. Methods sections of identified papers were reviewed to select all cohort studies that described an overall number of pregnant women contracting varicella and the number of children exhibiting CVS. Varicella infection could be confirmed by clinical appearance or serologic changes or both. Alkalay et al[1] have described criteria for CVS.

Excluded from the analysis were case reports, case series, editorials, and reviews, as were cohort studies describing women contracting herpes zoster (shingles) rather than varicella. Overall rate of CVS was calculated by pooling data in all studies. No attempt was made to

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Motherisk questions are prepared by the **Motherisk Team** *at the Hospital for Sick Children in Toronto, Ont.* **Dr Koren**, *a Senior Scientist at the Canadian Institutes for Health Research and Director of the Motherisk Program, is supported by the Research Leadership for Better Pharmacotherapy during Pregnancy and Lactation and, in part, by a grant from the Canadian Institutes for Health Research.*

Table 1. Incidence of congenital varicella syndrome in cohort studies

STUDY	FIRST TRIMESTER	SECOND TRIMESTER	THIRD TRIMESTER	OVERALL (%)
Siegal,[4] 1973	1/27	0/32	0/76	1/135 (0.74)
Paryani and Arvin,[5] 1986	1/11	0/11	0/19	1/41 (2.43)
Balducci et al,[6] 1992	0/35			0/35 (0)
Pasturszak et al,[7] 1994	1/86	0/30		1/116 (0.86)
Enders et al,[8] 1994	1/236	7/351		9/823 (1.09)
Jones et al,[9] 1994	1/110	1/46	0/13	2/169 (1.18)
Harger et al,[11] 2002	0/140	1/122	0/100	1/362 (0.28)
Hill,[2] 1958				0/30 (0)
Manson,[3] 1962				0/288 (0)
Figueroa-Damian and Arredondo-Garcia,[10] 1997				0/22 (0)
Mean (%)	5/645 (0.78)	9/592 (1.52)	0/208 (0)	14/2021 (0.7)*

**Not all studies classified data by trimester. Hence the sum of cases of first plus second plus third trimester is lower than the "overall" number.*

weight the data. Rates of CVS were compared by trimester of exposure using Fisher's exact test, as were rates among those receiving varicella zoster immune globulin (VZIG) versus others.

Between 1958 and 2002, 10 cohort studies[2-11] calculated the overall incidence of CVS among 2002 mother-child pairs (**Table 1**[2-11]). Seven studies also calculated incidence for each trimester of pregnancy. Overall rate of CVS was 14/2021 (0.7%) (95% confidence interval [CI] 0 to 5). The rate was 5/645 (0.78%) for first-trimester exposure, 9/592 (1.52%) for second-trimester exposure, and 0/208 (0%) for third-trimester exposure. The third-trimester rate was lower than the first- and second-trimester rates ($P < .01$). The trend toward higher rates in the second trimester than the first trimester (odds ratio 1.9) was not statistically significant ($P = .19$). Enders et al[8] described 92 women who received VZIG to prevent CVS; none of their babies contracted CVS, but nine among the 731 who did not receive VZIG did.

Based on 2021 available cases in 10 studies, incidence of CVS has been calculated at 0.7% with a trend toward more cases during the second trimester. It appears that CVS does not afflict fetuses during the third trimester. At present, seronegative women who have been in contact with someone with varicella are advised to take VZIG, which can be given by either intramuscular or intravenous injection.[12]

While the biologic plausibility of this treatment comes from favorable results in ameliorating or preventing clinical varicella in immunocompromised or otherwise healthy patients, no controlled studies show that VZIG prevents CVS. Our analysis reveals that the rate of CVS among 92 VZIG-treated mothers tended to be lower than among untreated mothers.[8] Because of the rarity of varicella infection in pregnancy in general and of CVS in particular, it is unlikely that a randomized controlled prospective study will have sufficient power to show a favourable effect of VZIG. Moreover, with VZIG being labeled for varicella infection in pregnancy, it is unlikely that ethics review boards will approve such a study.

With the recent introduction of a varicella vaccine,[13] it is likely that rates of seronegativity among women of reproductive age will gradually decrease, and hence incidence of CVS will likely decrease. While the overall rate of CVS among seronegative women exposed to the virus appears to be low, a 0.7% rate of CVS implies a substantially increased risk of major malformations above the 1% to 3% risk in the general population. For comparison, the rate of positive Down syndrome among women aged 35 is 1/350 (0.3%). ✦

References

1. Alkalay AL, Pomerance JJ, Rimoin DL. Fetal varicella syndrome. *J Pediatr* 1987;111:320-3.
2. Hill AB. Virus diseases in pregnancy and congenital defects. *Br J Prev Soc Med* 1958;12:1-7.
3. Manson J. *Rubella and other virus infections during pregnancy. Reports on public health and medical subjects No. 101.* Toronto, Ont: Ministry of Health; 1962.
4. Siegal M. Congenital malformations following chickenpox, measles, mumps and hepatitis. *JAMA* 1973;226:1521-4.
5. Paryani SG, Arvin AM. Intrauterine infection with varicella zoster virus after maternal varicella. *N Engl J Med* 1986;314(24):1542-6.
6. Balducci J, Rodis JF, Rosengren S, Vintzilosa M, Spiney G, Vosseller C. Pregnancy outcome following first trimester varicella infection. *Obstet Gynecol* 1992;79:5-6.
7. Pasturszak A, Levy M, Schick B, Zuber C, Feldman M, Gladstone J, et al. Outcome after maternal varicella infection in the first 20 weeks of pregnancy. *N Engl J Med* 1994;330:901-5.
8. Enders G, Miller E, Craddock Watson J, Bolley I, Ridenhelg M. Consequences of varicella and herpes zoster in pregnancy. *Lancet* 1994;343:1548-51.
9. Jones KL, Johnson KA, Chambers CD. Offspring of women infected with varicella during pregnancy: a prospective study. *Teratology* 1994;49:29-32.
10. Figueroa-Damian R, Arredondo-Garcia JL. Patient outcome of pregnancy complicated with varicella infection during the first twenty weeks of gestation. *Am J Perinatol* 1997;14:401-4.
11. Harger JH, Ernest JM, Thurman GR, Moawad A, Thom E, Landon MB, et al. Frequency of congenital varicella syndrome in a prospective cohort of 347 pregnant women. *Obstet Gynecol* 2002;100:260-5.
12. Koren G, Money D, Boucher M, Aoki F, Petric M, Innocencion G, et al. Serum concentrations, efficacy, and safety of a new, intravenously administered varicella zoster immune globulin in pregnant women. *J Clin Pharmacol* 2002;42:267-74.
13. Gershon AA. Varicella vaccine: rare serious problems—but the benefits still outweigh the risks. *J Infect Dis* 2003;188:945-7.

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