

# Smoking and Oral Clefts

**A**bout 1 in 4 California women smokes during pregnancy. Past studies hinted that smokers' babies may be more likely to have cleft lip and/or cleft palate, but results have been mixed.

This study by the California Birth Defects Monitoring Program is one of the first to consider babies' genes as well as mothers' smoking. Based on interviews with almost 1500 mothers, it includes 4 times more oral cleft cases than most previous studies on the subject. It also looks at smoke from multiple sources, including secondhand smoke.

## SMOKING DOUBLES RISK FOR CLEFTS

Mothers were asked about their smoking habits during the month before conception through the first 3 months of pregnancy. Those who smoked 20 or more cigarettes/day were more than 2 times as likely to have babies with cleft lip and/or cleft palate. Those who smoked less were about 1.5 times as likely to have babies with oral clefts.

For nonsmoking mothers, the effects of secondhand smoke were not clear-cut: there was little, if any, increased risk. Father's smoking increased the risk for oral clefts only if the mother smoked too.

## GENE VARIANT ALTERS SUSCEPTIBILITY

Are some infants genetically more susceptible to mothers' smoking? We looked at a gene normally involved in development of the palate and mouth—the transforming growth factor-alpha gene (TGF $\alpha$ ). Blood tests determined which of several forms of the gene babies inherited.

Infants with the A2 form of the TGF $\alpha$  gene were 8 times as likely to have oral clefts if their mothers smoked. Those born to nonsmoking mothers were at no greater risk. About 1 in 7 babies carries the A2 form of the TGF $\alpha$  gene.

## THE IMPACT OF ORAL CLEFTS

- Cleft lip and/or cleft palate occurs in 1 in 550 newborns—affecting about 1000 babies born in California annually and about 7000 nationwide.
- Babies with oral clefts require significant medical care—often 4 surgeries by age 2—and may have speech, hearing, and feeding problems.
- Average lifetime costs per case exceed \$100,000.
- 1 in 4 expectant mothers smokes—cutting out cigarettes during pregnancy could prevent 200 oral clefts each year in California.



## SMOKING AND OTHER FACTORS

- Smoking increased the risk for clefts whether or not babies had additional birth defects.
- The mother's age, race/ethnicity, or education did not significantly alter the effects of smoking.
- Using multivitamins did not mitigate the risk associated with smoking.

## BIOLOGICAL MECHANISM UNKNOWN

We do not know why a mother's cigarette smoking increases the risk for clefts in the developing fetus. Both carbon monoxide and nicotine—agents released through smoking—may lower the oxygen available to the fetus. Other components of cigarettes have been linked to birth defects in laboratory animals as well. We do not yet know why infants with the A2 form of the TGF $\alpha$  gene are more susceptible.

## POPULATION-BASED STUDY DESIGN

All cases were identified through ongoing surveillance by the California Birth Defects Monitoring Program registry, an actively ascertained, population-based database on children with birth defects.

Specific study elements follow:

- **Birth defects:** Cleft lip or palate or both. Infants with the chromosome abnormalities trisomy 21 (Down syndrome) or 45,X (Turner syndrome) were excluded. A medical geneticist classified cases according to the cleft type and whether additional birth defects were present.
- **Participants:** Mothers of infants or fetuses with clefts identified from 552,601 monitored births in 1987-1989, and a randomly selected comparison

group of mothers delivering infants without birth defects in the same years. Mothers of 731 oral cleft cases agreed to be interviewed—85% of those eligible. Interviews also took place with 734 mothers in the comparison group—78% of those eligible.

- **Diagnostic information:** Abstracted from hospital medical records, including surgical reports.
- **Interviews:** 40-minute telephone interviews in English or Spanish asking about environmental exposures during pregnancy.
- **Cigarette smoke exposure:** Mother's reported tobacco use. Each woman also was asked whether anyone smoked in her home or near her at work, school, or during other routine activities. She was asked how many cigarettes/day her baby's father smoked in the 3 months before and 3 months after conception.
- **Gene type:** Determined by analyzing DNA from residual newborn screening specimens; 85% of children were genotyped.

*REFERENCE: Shaw GM, Wasserman CR, Lammer EJ, O'Malley CD, Murray JC, Basart AM, Tolarova MM. Orofacial clefts, parental cigarette smoking, and transforming growth factor-alpha gene variants. American Journal of Human Genetics 1996;58(3): 551-561.*

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