

# **Do vasoactive exposures and vascular events affect the development of hemifacial microsomia?**

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Presented at the  
American Cleft Palate Craniofacial  
Association Meeting

Chicago, IL  
March 17, 2004

# **HFM Study**

## **Objectives:**

- 1) To identify vasoactive risk factors for hemifacial microsomia (medications, cigarette smoking, alcohol intake)**
- 2) To identify other risk factors**

# HFM Study

- 1997-2002
- Case control study
- Multicenter study – 26 cities in U.S. and Canada

# Cases

- From craniofacial specialists
- Hemifacial microsomia, facial asymmetry, Goldenhar syndrome, oculoauricular vertebral syndrome
- < 3 years of age
- Excluded chromosomal, Mendelian-inherited cases

# Controls

- From case's pediatrician or similar practice
- < 3 years of age
- Excluded subjects with malformations

# **Data collection**

- **Mothers were interviewed within 3 years after delivery**
- **By telephone**
- **About demographic, reproductive, medical, and behavioral factors**
- **Detailed questions on medication use**

# **Vasoactive Medication Use**

- **Pseudoephedrine**
- **Phenylpropanolamine (PPA)**
- **Aspirin**
- **Ibuprofen**

**during the first ten weeks of gestation,  
when HFM likely develops**

# Vasoactive exposures

- Alcohol:
  - Heavy -  $\geq 3$  drinks on  $\geq 3$  days/week in 1<sup>st</sup> tri.
  - Low -  $< 3$  drinks or  $< 3$  days/week in 1<sup>st</sup> tri.
- Smoking:
  - any smoking
  - High -  $\geq 10$ /day in 1<sup>st</sup> tri.
  - Low - 1-9/day in 1<sup>st</sup> tri.
- Amphetamine, cocaine in 1<sup>st</sup> tri.

# **‘Vascular’ Events**

- **Multiple gestation**
  - twins or triplets
- **Vaginal bleeding**
  - 1st trimester, 2nd trimester
- **Diabetes**
- **Hypertension**

# HFM Cases

**248 eligible HFM cases**

- 5 (2%) unable to contact
- 4 (2%) refused participation

**239 interviewed HFM cases**

- 9 (3%) unconfirmed diagnosis

**230 cases**

# Controls

**912 eligible non-malformed controls**

- 41 (5%) unable to contact
- 17 (2%) refused participation

**854 non-malformed controls**

- 176 (21%) unmatched controls

**678 controls**

# Results: Vasoactive Medications

Medication	HFM N (%)	Controls N (%)
Pseudoephedrine	43 (18.7)	82 (12.1)
PPA	5 (2.2)	8 (1.2)
Aspirin	14 (6.1)	24 (3.5)
Ibuprofen	28 (12.2)	50 (7.4)

# Results: Vasoactive Medications

Medication	Unadj. OR	Adj. OR (95 % CI)
Pseudoephedrine	1.7	2.0 (1.2-3.4)
PPA	1.9	0.8 (0.2-3.2)
Aspirin	1.8	1.5 (0.7-3.4)
Ibuprofen	1.8	1.7 (0.9-3.0)

# Results: Combined Vasoactive Medications

Medication	Unadj. OR	Adj. OR (95 % CI)
Vasoactive med use*	1.7	1.9 (1.2-2.9)

\*Pseudoephedrine, phenylpropanolamine, aspirin, or ibuprofen  
72 cases, 145 controls exposed

# Results: Vasoactive Exposures

Exposure	HFM N (%)	Controls N (%)
Alcohol - Low	81 (35.2)	272 (40.1)
- Heavy	4 (1.7)	3 (0.4)
Cigarette smoking	52 (22.6)	119 (17.6)
1-9/day	24 (10.4)	35 (5.2)
≥10/day	28 (12.2)	84 (11.9)
Cocaine/amphetam.	3 (1.3)	0 (0)

# Results: Vasoactive Exposures

Exposure	Unadj. OR	Adj. OR (95 % CI)
Alcohol $\geq 3, \geq 3$ d/w	3.7	6.2 (1.3-29.2)
Cigarette smoking	1.4	1.5 (0.9-2.3)
1-9/day	2.2	2.3 (1.2-4.4)
$\geq 10$ /day	1.0	1.2 (0.7-2.1)

# Results: Vasoactive Medication and Smoking

Exposure	Unadj. OR	Adj. OR (95 % CI)
Vasoactive med & no smoking	1.5	1.5 (1.0-2.5)
Smoking & no vaso- active med	1.2	1.1 (0.7-1.9)
<b>Both*</b>	<b>2.9</b>	<b>4.2 (2.0-8.9)</b>

\*20 cases and 24 controls exposed

# Results: Vascular Events

Event	HFM N (%)	Controls N (%)
Multiple gestation	21 (9.1)	8 (1.2)
Diabetes	18 (7.8)	10 (1.5)
Hypertension	8 (3.5)	16 (2.4)
Vaginal bleed. 1 <sup>st</sup> Tri	37 (16.1)	88 (13.0)
2 <sup>nd</sup> Tri.	8 (3.5)	2 (0.3)

# Results: Vascular Events

Event	Unadj. OR	Adj. OR (95 % CI)
Multiple gestation	8.4	10.5 (4.2-26.2)
Diabetes	5.7	6.0 (2.5-14.3)
Hypertension	1.5	1.2 (0.5-3.3)
Vag. bleed. 1 <sup>st</sup> Tri	1.3	1.0 (0.6-1.6)
2 <sup>nd</sup> Tri.	12.4	13.2 (2.3-75)

# HFM Subgroups

- Isolated
  - includes ear anomalies, vertebral anomalies, ocular dermoid, coloboma  
n=137
- Associated (HFM+) n=93
- Other vascular disruption defects (HFM+VDD) n=25

# HFM: Phenotypic variability

Event	Isolated	HFM+	HFM+ VDD
Vasoactive med.	1.8	2.0	5.5 (1.6-18.9)
Cigarette smoking	1.3	2.1	2.5
Multiple gestation	11.2	13.7	---
Diabetes	3.1	12.6	3.5
Hypertension	1.5	1.2	---
Vag. bleed. 2nd Tri	20.2	9.2	---

# **Study Limitations**

- **Study is not population-based**
- **Retrospective data collection**
- **Small numbers for some comparisons**
- **Phenotypic variability**

# Acknowledgements

NIDCR for funding

Jane Sheehan – Project Coordinator

Lisa Crowell – Interviewer

Katy Jones – Research Assistant

Lisa Knight – Research Assistant

Allen Mitchell – Co-investigator

Catherine Hayes – Co-investigator

John Mulliken – Co-investigator

Kathy Kelley – Research Pharmacist

**The Mothers**



**Slone**  
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## Acknowledgements: Multicenter Study

MA: Children's Hosp., Boston  
Baystate Med Ctr, Springfield  
NY: Buffalo Children's Hosp.  
NJ: The Cooper Health System  
PA: Children's Hosp. of Philadelphia  
MD: Johns Hopkins, Baltimore  
VA: Children's Hospital of King's  
Daughters, Norfolk  
NC: University of North Carolina  
Hosps, Chapel Hill  
SC: Medical University of S.C.  
GA: Children's Healthcare of Atlanta  
MI: Children's Hosp. of MI., Detroit  
OH: Children Hosp & Med Ctr, Akron  
Plastics & Reconst. Surgeons,  
Akron, Children's Hosp Columbus

IN: James W. Riley Hosp. for  
Children, Indianapolis  
WI: Children's Hosp. of WI, Milwauk.  
IA: University of Iowa, Iowa City  
MO: Saint Louis Children's Hosp.  
LA: Children's Hosp. of New Orleans  
Ochsner Foundation Hosp., N.O.  
AZ: Saint Joseph's Med Ctr, Phoenix  
Southwest Craniofacial Ctr,  
Phoenix  
TX: Texas Children's Hosp., Houston  
Children's Medical Ctr, Dallas  
CA: Children's Hosp. of L.A.  
WA: Children's Hosp & Med Ctr,  
Seattle  
CAN.: Hosp. for Sick Children, Toron.  
Alberta Children's Hosp, Calgary