

**Appendix**

**Presentation 1- Maria Araneta**

**Birth Defects and Pregnancy Outcomes  
Following Service in the Gulf War**

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October 27, 2003

Meeting of the Research Advisory Committee  
on Gulf War Veterans' Illnesses

**Prevalence of Birth Defects Among  
Infants of Gulf War Veterans in Arkansas,  
Arizona, California, Georgia, Hawaii, and  
Iowa, 1989-1993**

*Birth Defects Research (Part A): Clinical and  
Molecular Teratology 2003: 67;246-260*

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**Background**

- U.S. General Accounting Office: 21 teratogens and reproductive toxicants present in the GW environment
- *Oil fires and soil:*
  - arsenic      benzene      benzopyrene
  - cadmium    lead          mercury
  - nickel      toluene      xylene
  - di-n-butyl phthalate      hexachlorobenzene
  - hexachloroethane      pentachlorophenol
  - hexachlorocyclopentadiene
- *Pesticides:*
  - carbaryl                      diazinon      dichlorvos
  - ethanol                      lindane      warfarin
- *Decontaminating agents:*
  - ethylene glycol monomethyl ether

### Previous studies

- *Penman, 1996: 2 National Guard units, 5 case infants*
- *Cowan, 1997: military hospitals, newborn diagnoses only, ICD-9 codes*
- *Araneta, 1997: Goldenhar syndrome, military hospitals, rare condition*
- *Goss Gilroy, Inc. 1998: Canada, self-reported, † birth defects among GWV infants*
- *Kang, 2001: self-reported, not validated against medical records, † birth defects among GWV infants*

### States with Active Surveillance for Birth Defects



### Active Case Ascertainment for Birth Defects

1. Population-based
  - includes military and non-military hospitals
  - births to Reservists and National Guard members
  - births to former military personnel
2. Surveillance through infant's 1st birthday
  - Captures 95%-99% of birth defects

### Active surveillance of Birth Defects

3. Data abstracted from multiple sources:
  - outpatient clinics*                      *hospitals*
  - cytogenetic laboratories*              *genetic clinics*
  - cardiac catheterization logs*              *surgical logs*
  - molecular biology laboratories*
4. Birth defects recorded by CDC's 6-digit code for Reportable Congenital Anomalies
5. Provides more complete case ascertainment and morphologic classification of birth defects

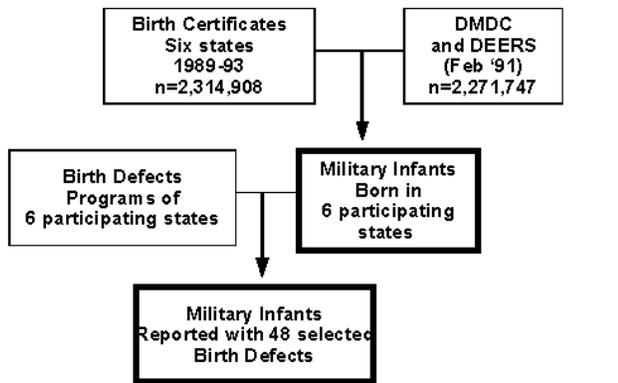
### Objectives

- Identify infants born to military personnel between 1989-93 in states with active surveillance of birth defects
- Measure the prevalence of selected birth defects
  - a) GWV and NDV infants
    - prewar conceptions
    - postwar conceptions
  - b) GWV infants
    - prewar vs. postwar conceptions

### Methods - Data Sources

- Military:**
- Defense Manpower Data Center (DMDC) - *military sponsor data*
  - Defense Eligibility Enrollment Reporting System (DEERS) - *spouse, children*
- Arkansas, Arizona, California, Georgia, Hawaii, Iowa:
- Vital records - *birth certificates*
  - Birth Defects Programs - *birth defects data*

### Military Infants in the participating states Birth Defects Registries



### 48 Selected Birth Defects

- |                             |                     |
|-----------------------------|---------------------|
| Anencephalus                | Spina Bifida        |
| Hydrocephalus               | Encephalocele       |
| Microcephalus               |                     |
| Aniridia                    | Congenital cataract |
| Anophthalmia/microphthalmia |                     |
| Anotia/microtia             |                     |
| Cleft palate                | Cleft lip           |

**48 Selected Birth Defects (continued)**

|                                  |                      |
|----------------------------------|----------------------|
| Common truncus                   | Tetralogy of Fallot  |
| Ventricular septal defect        | Ebstein's anomaly    |
| Aortic valve stenosis            | Coarctation of aorta |
| Pulmonary valve atresia/stenosis |                      |
| Pulmonary valve insufficiency    |                      |
| Endocardial cushion defect       |                      |
| Pulmonary artery anomalies       |                      |
| Transposition of great arteries  |                      |
| Tricuspid atresia/stenosis       |                      |
| Tricuspid valve insufficiency    |                      |
| Hypoplastic left heart syndrome  |                      |

**48 Selected Birth Defects (continued)**

|  |                      |
|--|----------------------|
| Lung agenesis/hypoplasia                     | Choanal atresia      |
| Pyloric stenosis                             | Hirschsprung disease |
| Biliary atresia                              | Gastroschisis        |
| Diaphragmatic hernia                         | Omphalocele          |
| Hypospadias/epispadias                       | Bladder exstrophy    |
| Renal agenesis/hypoplasia                    |                      |
| Obstructive genitourinary defect             |                      |
| Esophageal atresia/tracheoesophageal fistula |                      |
| Rectal/large intestinal atresia/stenosis     |                      |

**48 Selected Birth Defects (continued)**

Reduction deformity - upper limbs, lower limbs  
 Trisomy 13 (Patau syndrome)  
 Trisomy 18 (Edward syndrome)  
 Trisomy 21 (Down syndrome)

|  |                              |
|--|------------------------------|
| Fetal alcohol syndrome                                     | Amniotic bands               |
| <i>Dextrocardia</i>  | <i>Chromosomal anomalies</i> |
| <i>Goldenhar syndrome (oculoauriculovertebral complex)</i> |                              |

**Estimates of Prewar and Postwar Conceptions**

Prewar conceptions:

GWV: Infant's DOB  $\leq$  Mother's deployment date  
 Infant's DOB - gest. age  $\leq$  Father's deploy date  
 NDV: Conceived  $\leq$  December 31, 1990

Postwar conceptions:

GWV: Infant's DOB  $>$  Mother's deployment date  
 Infant's DOB - gest. age  $\geq$  Father's return date  
 NDV: Conceived  $\geq$  January 1, 1991

**Table 1. Demographic Characteristics of Infants Born to Women Military Personnel, 1989-93**

|                         | <u>GWV<br/>(n=450)</u> | <u>NDV<br/>(n=3,966)</u> |
|-------------------------|------------------------|--------------------------|
| Male                    | 48%                    | 50%                      |
| Birthweight (gms)       | 3,351                  | 3,341                    |
| Preterm birth (<37 wks) | 9%                     | 9%                       |
| Maternal age (yrs)      | 25.3                   | 25.9*                    |
| Paternal age (yrs)      | 27.2                   | 27.5                     |
| White                   | 51%                    | 60%*                     |
| ≤ High school           | 55%                    | 53%                      |
| Unmarried               | 28%                    | 23%*                     |

\*p-value<0.05 (statistically significant)

**Demographic Characteristics of Infants Born to Women Military Personnel, 1989-93**

|                      | <u>GWV<br/>(n=450)</u> | <u>NDV<br/>(n=3,966)</u> |
|----------------------|------------------------|--------------------------|
| Smoking              | 7%                     | 9%                       |
| Alcohol              | 1%                     | 1%                       |
| Prenatal visits      | 11.2                   | 11.7*                    |
| Army                 | 64%                    | 35%*                     |
| Marine Corps         | 11%                    | 5%*                      |
| Reservist/Natl Guard | 24%                    | 12%*                     |
| Military Officers    | 8%                     | 11%*                     |

\*p-value<0.05

**Table 2. Demographic Characteristics of Infants Born to Male Military Personnel, 1989-93**

|                        | <u>GWV<br/>(n=11,511)</u> | <u>NDV<br/>(n=29,086)</u> |
|------------------------|---------------------------|---------------------------|
| Birthweight (gms)      | 3,367                     | 3,389*                    |
| Maternal age (yrs)     | 25.3                      | 26.0*                     |
| Paternal age (yrs)     | 26.6                      | 27.5*                     |
| White (mother)         | 59%                       | 63%*                      |
| ≤ High school (mother) | 56%                       | 51%*                      |
| Unmarried              | 10%                       | 7%*                       |
| Prior live births      | 0.8                       | 0.9*                      |
| Multiple births        | 1.8                       | 2.4*                      |

\*p-value<0.05

**Demographic Characteristics of Infants Born to Male Military Personnel, 1989-93**

|                    | <u>GWV<br/>(n=450)</u> | <u>NDV<br/>(n=3,966)</u> |
|--------------------|------------------------|--------------------------|
| Marine Corps       | 28%                    | 11%*                     |
| Enlisted personnel | 83%                    | 78%*                     |

\*p-value<0.05

**Table 3. Selected Birth Defects Prevalence\* among Prewar conceptions to Women GWVs and NDVs, 1989-91**

|                        | GWV<br>(n=142) | NDV<br>(n=2,007) | RR (95% CI)  |
|------------------------|----------------|------------------|--------------|
| Hydrocephalus          | 1 (70)         | 2 (10)           | 7.1 (0.6-79) |
| VSD                    | 0              | 11 (55)          |              |
| <b>Obstructive</b>     |                |                  |              |
| genitourinary defect   | 0              | 6 (30)           |              |
| Pyloric stenosis       | 0              | 5 (30)           |              |
| Hypospadias            | 0              | 5 (30)           |              |
| Tetralogy of Fallot    | 0              | 4 (20)           |              |
| Cleft lip w/o c.palate | 0              | 3 (15)           |              |

\*per 10,000 live births

**Table 4. Selected Birth Defects Prevalence\* among Prewar conceptions to Male GWVs and NDVs, 1989-91**

|                               | GWV<br>(n=6,863) | NDV<br>(n=17,922) | RR (95% CI)     |
|-------------------------------|------------------|-------------------|-----------------|
| Hypospadias                   | 22 (32)          | 51 (29)           | 1.1 (0.7 - 1.9) |
| Pyloric stenosis              | 14 (20)          | 25 (14)           | 1.5 (0.8 - 2.8) |
| VSD                           | 13 (19)          | 45 (25)           | 0.8 (0.4 - 1.4) |
| <b>Obstructive</b>            |                  |                   |                 |
| genitourinary defects         | 9 (13)           | 29 (16)           | 0.8 (0.4 - 1.7) |
| Down syndrome                 | 9 (13)           | 21 (12)           | 1.1 (0.5 - 2.5) |
| Tricuspid valve insufficiency | 8 (18)           | 24 (20)           | 0.9 (0.4 - 2.0) |
| Aortic valve stenosis         | 0                | 4 (2)             |                 |

\*per 10,000 live births

**Table 5. Selected Birth Defects Prevalence\* Among Postwar Conceptions to Women GWVs and NDVs, 1991-93**

|                    | GWV<br>(n=308) | NDV<br>(n=1,959) | RR (95% CI)                 |
|--------------------|----------------|------------------|-----------------------------|
| Hydrocephalus      | 1 (32)         | 1 (5)            | 6.4 (0.2 - 189)             |
| VSD                | 1 (32)         | 7 (36)           | 0.9 (0.05 - 5.5)            |
| Pulm valve atresia | 1 (32)         | 1 (5)            | 6.4 (0.2 - 189)             |
| Cleft lip          | 1 (32)         | 1 (5)            | 6.4 (0.2 - 189)             |
| Hypospadias        | 4 (130)        | 4 (20)           | 6.4 (1.5 - 27) <sup>†</sup> |
| Renal agenesis     | 1 (32)         | 3 (15)           | 2.1 (0.1 - 18)              |
| Obst genitourinary | 1 (32)         | 8 (41)           | 0.8 (0.04 - 4.7)            |
| <br>               |                |                  |                             |
| Down syndrome      | 1 (32)         | 0                |                             |

\*per 10,000 live births; <sup>†</sup>p = 0.015

**Table 6. Selected Birth Defects Prevalence\* Among Postwar Conceptions to Male GWVs and NDVs, 1991-93**

|                                 | GWV<br>(n=4,648) | NDV<br>(n=11,164) | RR (95% CI)                 |
|---------------------------------|------------------|-------------------|-----------------------------|
| Hypospadias                     | 15 (32)          | 35 (31)           | 1.0 (0.6 - 2)               |
| VSD                             | 10 (24)          | 36 (32)           | 0.7 (0.3 - 1)               |
| Tricuspid valve insufficiency** | 10 (29)          | 9 (11)            | 2.7 (1.1 - 7) <sup>†</sup>  |
| Obst genitourinary              | 9 (19)           | 21 (19)           | 1.0 (0.5 - 2)               |
| Pyloric stenosis                | 7 (15)           | 18 (16)           | 0.9 (0.4 - 2)               |
| Aortic valve stenosis           | 5 (11)           | 2 (2)             | 6.0 (1.2 - 31) <sup>‡</sup> |
| Coarctation of aorta            | 5 (11)           | 3 (3)             | 4.0 (0.96-17)               |
| Renal agenesis                  | 5 (11)           | 5 (4)             | 2.4 (0.7 - 8)               |

\*per 10,000 live births, \*\* California births excluded, <sup>†</sup>p=0.039, <sup>‡</sup>p=0.026

**Table 7. Selected Birth Defects Prevalence\* Among Prewar vs. Postwar conceptions to Women GWVs, 1989-93**

|                    | Postwar<br>(n=308) | Prewar<br>(n=142) | RR (95% CI)    |
|--------------------|--------------------|-------------------|----------------|
| Hydrocephalus      | 1 (32)             | 1 (70)            | 0.5 (0.03 - 7) |
| VSD                | 1 (32)             | 0                 |                |
| Pulm valve atresia | 1 (32)             | 0                 |                |
| Cleft lip          | 1 (32)             | 0                 |                |
| Hypospadias        | 4 (130)            | 0                 |                |
| Renal agenesis     | 1 (32)             | 0                 |                |
| Obst genitourinary | 1 (32)             | 0                 |                |
| Down syndrome      | 1 (32)             | 0                 |                |

\*per 10,000 live births

**Table 8. Selected Birth Defects Prevalence\* Among Prewar vs. Postwar conceptions to Male GWVs, 1989-93**

|                                 | Postwar<br>(n=4,648) | Prewar<br>(n=6,863) | RR (95% CI)     |
|---------------------------------|----------------------|---------------------|-----------------|
| Hypospadias                     | 15 (32)              | 22 (32)             | 1.0 (0.5 - 2)   |
| VSD                             | 10 (21)              | 13 (19)             | 1.1 (0.5 - 3)   |
| Tricuspid valve insufficiency** | 10 (29)              | 8 (18)              | 1.6 (0.6 - 4)   |
| Obst genitourinary              | 9 (19)               | 9 (13)              | 1.5 (0.6 - 4)   |
| Pyloric stenosis                | 7 (15)               | 14 (20)             | 0.7 (0.2 - 2)   |
| Aortic valve stenosis           | 5 (11)               | 0                   | 16 (0.9 - 294)† |
| Coarctation of aorta            | 5 (11)               | 1 ( 2)              | 7.4 (0.9 - 63)  |
| Renal agenesis                  | 5 (11)               | 0                   | 16 (0.9 - 294)† |

\* per 10,000 live births; † p<0.011 logit estimator

**Adjusted Prevalence – cardiovascular defects**

↑ tricuspid valve insufficiency and aortic valve stenosis did not differ when adjusted by:

- State
- Maternal and paternal age
- Ethnicity
- Marital Status
- Education
- Parity, multiple births
- Prenatal visits
- Military branch, rank

**Adjusted Prevalence – hypospadias**

↑ Prevalence of hypospadias persisted after adjustment for:

- Paternal age
- Small for gestational age
- Low birth weight
- Preeclampsia
- Low parity

### **Adjusted Prevalence – renal agenesis or hypoplasia**

- ↑ Prevalence of renal agenesis/hypoplasia persisted after adjustment for:
- Prenatal alcohol
  - Intrauterine growth retardation

### **Conclusions**

- Linkage of military and state health department records enables measurement of the prevalence of birth defects among infants:
  - Through infant's 1<sup>st</sup> year of life
  - in military and civilian hospitals
  - Reservists and National Guard members
  - former and current military personnel
- Higher prevalence of tricuspid valve insufficiency, aortic valve stenosis, and renal agenesis/hypoplasia in postwar infants of GWV men.

### **Conclusions**

- Higher prevalence of hypospadias among postwar infants of GWV women.
- The etiology of birth defects is unknown for 70% of all birth defects
- We did not have the ability to determine if the excess risk of birth defects was caused by inherited, environmental, or synergistic factors, or was due to chance.

### **Limitations**

- California: no access to military hospitals
- Limited to live births
- Birth defects diagnosed after first birthday not included (1% - 5%)
- Statistical power
- Multiple comparisons

### Statistical Power

| <u>Condition</u>        | <u>Optimum<br/>sample size</u> | <u>Available</u> |
|-------------------------|--------------------------------|------------------|
| Hypospadias             | 257                            | 154              |
| Statistical power       | 80%                            | 67%              |
| Tricuspid valve insuff. | 6373                           | 4648             |

### Multiple Comparisons

| <u>Comparisons</u>            | <u>Expected</u> | <u>Observed</u> |
|-------------------------------|-----------------|-----------------|
| Postwar GWV vs NDV women      |                 |                 |
| 7 birth defects               | 0.35            | 1               |
| Postwar GWV vs NDV men        |                 |                 |
| 26 birth defects              | 1.3             | 2               |
| Postwar GWV vs prewar GWV men |                 |                 |
| 24 birth defects              | 1.2             | 2               |

### Conception and Pregnancy during the Persian Gulf War: The Risk to Women Veterans

Annals of Epidemiology, November 2003

Araneta MRG, Kamens DR, Zau AC, Gastanaga VM, Schlangen KM, Hiliopoulos KM, Gray GC.

### Purpose

To characterize reproductive outcomes:

- Live births
  - Stillbirths
  - Spontaneous abortions
  - Ectopic pregnancies
  - Induced abortions
- among women who were pregnant while deployed to the Gulf War

### Methods

- Deployment data + inpatient records (153 military hospitals) were used to identify servicewomen who were:
  - pregnant between August 1990 and May 1992
  - belonged to UIC deployed to the Gulf War
- Postal surveys in 1997-98 to elicit reproductive history + individual deployment dates
- Validated self-reported outcomes against military hospitalization records

### Results

- 3285 women had a pregnancy-related admission in a military hospital
- 1558 completed the questionnaire

Dates of delivery (or fetal loss), weeks of gestation, and individual deployment dates identified:

415 Gulf-war exposed pregnancies  
298 GWV postwar conceptions  
427 NDV conceptions

### Results

- The prevalence of stillbirths, spontaneous abortions, ectopic pregnancies, and induced abortions were similar among GWV-exposed pregnancies and NDV conceptions.
- Spontaneous abortions were significantly higher among postwar GWV conceptions (22.8%) compared to NDV conceptions (9.1%, adjusted OR: 2.92, 95% CI: 1.9 – 4.6)
- Ectopic pregnancies were significantly higher among postwar GWV conceptions (10.7%) compared to NDV conceptions (1.4%, adjusted OR: 7.7, 95% CI: 3.0 -20)

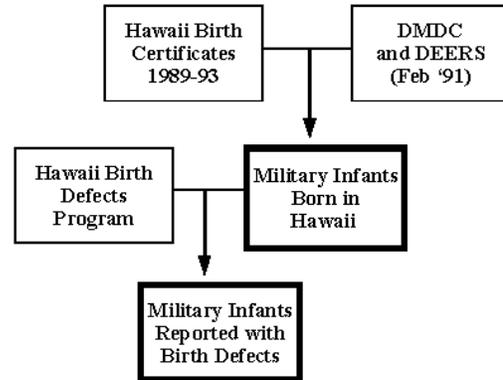
### Conclusions

- Among women veterans who belonged to units that were deployed to the Gulf War:
- GWV-exposed conceptions and nondeployed conceptions had similar reproductive outcomes.
- However, GWV postwar conceptions were at increased risk for ectopic pregnancies and spontaneous abortions

### Selection of Hawaii for Pilot Site

- Large military population
  - 20% of births have a military parent
- Same genetic referral site for military and civilian hospitals
- Parental SSN on birth certificate
- Military employment on birth certificate

### Military Infants Reported to the Hawaii Birth Defects Program



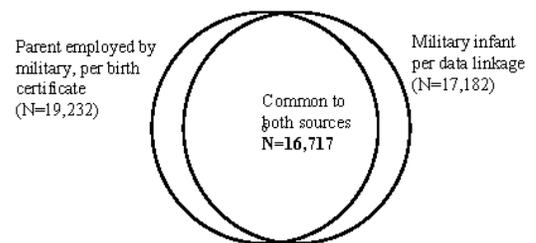
### How to improve statistical power? How to reduce multiple comparisons?

|                                 | GWV<br>(n=4,956) | NDV<br>(n=13,123) | RR (95%CI)                   |
|---------------------------------|------------------|-------------------|------------------------------|
| Tricuspid valve insufficiency** | 10 (27)          | 10 (10)           | 2.6 (1.1 – 6.4) <sup>†</sup> |
| Aortic valve stenosis           | 5 (10)           | 2 ( 1.5)          | 6.6 (1.4 - 45) <sup>‡</sup>  |
| Coarctation of aorta            | 5 (10)           | 3 ( 2)            | 4.4 (1.1 - 21) <sup>§</sup>  |

\*per 10,000 live births, \*\* California births excluded,  
<sup>†</sup>p=0.023, <sup>‡</sup>p=0.019, <sup>§</sup>p=0.04

27 comparisons, expect 5% (1.4) to differ due to chance, observe differences in 3

### Enumeration of Military Infants: Military Employment on Birth Certificate vs. Linkage Method, Live Births, Hawaii, 1989-93



Sensitivity = 87%    Specificity = 99%    Positive Predictive Value = 97%