

Presentation 8 – Beatrice Golomb

**Birth Defects
6-03**

B. Golomb, MD, PhD

1994 GAO report

**21 potential reproductive toxins in the Gulf
Unclear result of multiple agents: including
insecticide, petroleum solutions, sandstorm
dust, arthropod-borne pathogens, sarin,
mustard gas, prophylactic drugs and meds,
vaccines to military.**

Review

**Previous epi studies show paternal exposure
to pesticides, solvents, metals associated
with spina bifida, cardiac and renal defects,
cleft lip and palate, clubfoot.**

**Paternal herbicide exposure positively
correlated with spina bifida, per IOM report
on health effects of Vietnam veterans to
herbicide exposure (1996)**

IOM 1996. Araneta 1997 Teratology 56: 244-51

Specialized studies

**Penman 1996: no link Mississippi Natl Guard
Araneta 1997: no link to Goldenhar syndrome
Araneta 1997: no link Hawaiian GWV
Ishoy 2001: no link Danish GWV
(661 deployed, 215 nondeployed military men)**

GWV - Gulf War veterans

1997: Goldenhar syndrome

In response to press suggestions of birth defects -- especially Goldenhar*

Goldenhar = oculoauriculovertebral. Microtia, ear tags, or anotia, & variable eye, face, spine

Military hospital births post GWV to 10-93
 34,069 GWV infants; 41,345 NDV infants

7 with Goldenhar: 5 GWV, 2 NDV. All fathers in military at conception and birth

14.7/100,000 live births GWV (5.4-36.4)
 4.8/100,000 NDV (0.8-19.5) (NDV=nondeployed veterans)

RR = 3.03, 0.63-20.57, p = 0.26

Araneta 1997 Teratology 56:244-51. Cites Briggs 1995 & Sylvester 95

Hawaiian GWV

Goal: Examine specific birth defects

Sample: Link personal identifiers of GWV (n=684,645) and NDV (1,587,102) and families against live births in Hawaii Dept of Health 1989-93

Subjects: 3717 GWV infants; 13,465 NDV infants

Results:
 367 (2.14/100 live births) identified with ≥1 major birth defect dx

Similar prevalence for GWV & NDV prewar and postwar; and GWV infants conceived before & after the war

BUT small # each birth defect category

Araneta 2000 Teratology 62:195-204

Cowan

Subjects: Military hospital live births (135 military hospitals)
 Live births before 10-1-1993 (1991, 1992, 1993) with est conception after return from PG.
 For nondeployed: as above but est date conception after 12-31-90.
 Each birth, including each of multiple births, was treated as an independent event
 N=30,151 to wives of 29,468 male GWV; 32,638 to wives of 31,646 NDV
 N=3847 to 3722 female GWV; and 8825 to 8494 female NDV

Outcome: Birth defects as noted in the medical file. Also, ratio M:F.
Exposure: Days of deployment - no association; interval from return to birth.

Comment: Afr Amer and single more likely to report 'any birth defect'
 Navy less likely and army more likely to be deployed.
 Adjustment for race/ethnic, marital status, branch of service; age At Delivery!

Adjustment: Age at delivery [should be at conception]; race; ethnicity; marital status
 Cowan DN et al. The risk of birth defects among children of Persian Gulf War veterans. NEJM 1997 336:1650-6.

Cowan

	SEVERE BIRTH DEFECTS: RR (95% CI)	
	Crude	Adjusted
Active Duty Men	1.03 (.92-1.15)	NOT GIVEN!
Active Duty Women	1.00 (.90-1.10)	NOT GIVEN!
	ALL BIRTH DEFECTS: RR (95% CI)	
	Crude	Adjusted
Active Duty Men	.99 (.93-1.05)	.97 (.91-1.03)
Active Duty Women	1.12 (1.00-1.25)	1.07 (.94-1.22)

Adjustment: Age at delivery [should be at conception]; race; ethnicity; marital status
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DoD birth defects registry

Established Naval Health Research Center, San Diego, in 1998.
 Captures comprehensive data on healthcare utilization to calc prevalence of birth defects in children of military beneficiaries.
 Population-based electronic surveillance supplemented by active case validation.
 Has captured (by publication) data on >90,000 births in military families each year.
 Detailed analyses linking with exposure data, e.g. anthrax vaccination, are under way.
 Ryan M.A.K. 2001. Teratology 64:S26-29. The Dept of Defense birth defects registry: Overview of a new surveillance system.

More on DoD birth defects registry

Compared health record abstraction (active surveillance) with screening electronic medical data (passive surveillance) to detect birth defects among San Diego County military families from 1-1-97 to 6-30-98.
 171 of 5351 infants (3.2%) identified with major defect. C/w national civilian rates.
 ~80% concordance between “passive” and “active” approaches suggesting use of hybrid with electronic supplemented by active surveillance in a specific region.
 Bush R.A. 2001. Military Medicine 166: 2:179. Active surveillance of birth defects among US Dept of Defense beneficiaries: A feasibility study

Kang Study: Reproductive Outcomes

Subjects: 15,000 GWV; 15,000 era veterans. Stratified random sample. Actually: 3397 GWV; 2646 Era 'had an index pregnancy'. 4712 men. 1331 women.
Design: Mailed 16 page Health survey
Included questions on: fetal death (miscarriage <20wk, stillbirth>20wk, other); gestational length; death within 1 year. (Not elective abortions.)
Examined 1 pregnancy per veteran (vs each birth counted separately), the first ending after June 30, 1991
 Kang H et al 2001. Pregnancy outcomes among US Gulf War veterans: a population-based survey of 30,000 veterans. *Ann Epidemiol* 11:504-511.

Kang Study: Reproductive Outcomes

Outcome	GWV	ERA	OR	ADJ
Pregnancies				
Male	2739	1934		
Female	632	691		
Live Births				
Male	2236	1689	.64* (.54-.76)	.64* (.55-.76)
Female	471	577	.58 (.44-.76)	.60 (.46-.79)
Stillbirth				
Male	38	16	1.69 (.91-3.16)	1.65 (.91-2.98)
Female	9	7	1.41 (.48-4.22)	1.26 (.46-3.49)
Spont Abortions				
Male	327	148	1.64(1.33-2.02)	1.62 (1.32-1.99)
Female	92	77	1.36 (.97-1.90)	1.35 (.97-1.89)

Adjusted: race, age at outcome, ground vs non troop, active military vs Nat Guard or Reserves; hx smoking; hx prior pregnancy; calendar yr of pregnancy outcome.
 Kang H et al 2001. Pregnancy outcomes among US Gulf War veterans: a population-based survey of

Kang Study: Reproductive Outcomes				
<u>Outcome:</u>	GWV	ERA	OR	ADJ
Other* (could include elective abortion, currently pregnant)				
Male	138	81	1.21 (.91-1.62)	1.29 (.96-1.72)
Female	60	30	2.31 (1.44-3.73)	2.18 (1.37-3.46)
Adjusted: race, age at outcome, ground vs non troop, active military vs Nat Guard or Reserves; hx smoking; hx prior pregnancy; calendar yr of pregnancy outcome.				
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Kang Study: Reproductive Outcomes				
<u>Outcome:</u>	GWV	ERA	OR	ADJ
Pre-term				
Male	233	150	1.21 (.97-1.51)	1.2 (.97-1.5)
Female	61	69	1.08 (.73-1.59)	.99 (.68-1.45)
Birth Defects				
Male	202	68	2.37 (1.77-3.17)	2.34 (1.76-3.10)
Female	41	21	2.52 (1.43-4.49)	2.85 (1.62-4.99)
Likely Defects				
Male	120	47	1.98 (1.39-2.83)	1.94 (1.37-2.74)
Female	26	13	2.53 (1.23-5.27)	2.97 (1.47-5.99)
Mod to severe				
Male	82	35	1.80 (1.18-2.74)	1.78 (1.19-2.66)
Female	19	10	2.38 (1.04-5.56)	2.8 (1.26-6.25)
Adjusted: race, age at outcome, ground vs non troop, active military vs Nat Guard or Reserves; hx smoking; hx prior pregnancy; calendar yr of pregnancy outcome.				

Kang Study: Reproductive Outcomes				
<u>Outcome:</u>	GWV	ERA	OR	ADJ
Infant deaths (<1yr), all causes				
Male	12	12	0.75 (.32-1.79)	0.76 (.34-1.72)
Female	3	6	0.61 (.12-2.75)	0.80 (.19-3.38)
Adjusted: race, age at outcome, ground vs non troop, active military vs Nat Guard or Reserves; hx smoking; hx prior pregnancy; calendar yr of pregnancy outcome.				
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Adjusted: race, age at outcome, ground vs non troop, active military vs Nat Guard or Reserves; hx smoking; hx prior pregnancy; calendar yr of pregnancy outcome.				
Occurrence among 4973 live births: GWV male 2236; Era male 1689; GWV female 471; Era female 577.				
Kang H et al 2001. Pregnancy outcomes among US Gulf War veterans: a population-based survey of 30,000 veterans. <i>Ann Epidemiol</i> 11:504-511.				

Kang Study: Breakdown of defects

Percent infants with defect:	GW%	Era%
Total	5.39	2.65
Isolated anomaly (*X chromosomal & Heritable)	4.1	1.77
Multiple anomalies*	.26	.49
Undescribed isolated cardiac abnormality	.48	.22
Chromosomal	.26	0.0
Congenital malignancy	.04	0.0
Heritable genetic disease	.11	0.0
Other poorly described noncardiac defect	.15	.18

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 Kang H et al 2001. Pregnancy outcomes among US Gulf War veterans: a population-based survey of 30,000 veterans. *Ann Epidemiol* 11:504-511.

UK reproductive outcomes study

Design: Postal questionnaire, retrospective cohort study of UK GWV vs nondeployed, to 25,085 GWV (24379 men); 19,003 era (18439 men).

Ss: 16442 GWV/11517 era, men. 484 GWV/ 377 era, women.

Response rate[^]: Men: 53% GWV, 42% era. Women 72% GW, 60% era.

Data: All liveborn children: congen defects; serious med conditions ever; death date. Fertility/miscarriage/ectopic pregnancy. Abortions & abnormalities in conceptus. Participant's health. Partner's health. Changes in health since 1991. Info on any partner with whom conceived pregnancies who ever served in Armed Forces.

Missing info: checked by letter or phone. * **Macnochie N**

[^]A adjusted for undelivered mail. Nonresponder study: response status unrelated to reprod.

UK reproductive outcomes

- ICD 10 code for congen anomalies done blinded.
 - Clinical verification of reported conditions: asked for detail of doctor of mother of all reported pregnancies and of children. Asked permission to access medical notes.
 - Fetal deaths: Male*: 77 GWV:60 NDV. RR= 0.90
 - Miscarriage ≥16 weeks: 175:127 (not divided by sex): RR= 0.97
 - Congen malformation, M*: 686:342, RR1.41(p=0.07)
 - Congenital malformation, female
 - ? If selection bias. Low response rate.
- * Veteran was male
 • Macnochie N et al. BMC Public Health 2003, 3:4.

UK birth defects (all): Male veteran

DEFECT	RR	GW 16442	ERA 11517
Metab & sgl gene	1.94	22	8
Musculoskeletal	1.75	194	78
Other, none'somal	1.66	45	19
Genital system	1.66	45	19
Urinary system	1.51	103	48
Any congen malfor	1.41	686	342
Digestive system	1.37	72	37
CNS	1.36	58	30
Cranial neural crest	1.36	184	101
Eye, ear, neck, face	1.29	22	12
Circulatory	1.20	126	74
Respiratory	1.06	18	12
Cleft lip/palate	1.05	21	14
Chromosomal	0.86	49	40

UK birth defects (confirmed): Male vet

DEFECT	RR	GW 16442	ERA 11517
Metabolic & single gene	1.23	7	4
Musculoskeletal	1.44	92	45
Other, non chromosomal	1.03	22	15
Genital system	1.12	19	12
Urinary system	1.49	55	26
Any congenital malformation	1.18	330	196
Digestive system	1.09	31	20
CNS	1.12	27	17
Cranial neural crest	1.13	92	57
Eye, ear, neck, face	1.17	10	6
Circulatory	0.92	60	46
Respiratory	2.10	9	3
Cleft lip/palate	Infin	14	0

UK birth defects (all): Female veteran

Maconochie N et al BMC Public Health 2003, 3:4.

- All birth defects (combined, due to small N)

	RR	GW, n= 705	ERA, n= 564
All	1.69	19	9
Confirmed	1.60	10	5

US birth defects

Design: link military & birth certificate records

Subjects: 11961 GWV infants; 33052 NDV infants

- 684,645 GWV and 1587,102 NDV military records
- 2,314,908 birth certificate records from states with active ascertainment

48 diagnoses considered:

- 46 diagnoses routinely obtained by states.
- Excluded pulm artery anomalies: require dx'ic echo
- Added items of concern to veterans: Goldenhar's, chromosomal, & dextrocardia.

Araneta, M.R.G. et al Birth Defects Research 67: 246-260 2003. Prevalence of birth defects among infants of Gulf War veterans in Arkansas, Arizona, California, Georgia, Hawaii, and Iowa, 1989-1993

US birth defects

Design: Link military & birth certificate records from states that conducted active case ascertainment on birth defects from 1989-1993.

Subjects: 11961 GWV infants; 33052 NDV infants
 450 GWV mother; 3966 NDV mother

Drawn from:

- 684,645 GWV and 1587,102 NDV military records
- 2,314,908 birth certificate records from states with active ascertainment

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US birth defects

Mother's Age: Younger in GWV than NDV
 25.3 v 25.9 yrs, Vet. Mom *; 25.3 vs 26.0* Vet. Dad
 Age >35: 3.6 v 6.5%, Vet. Mom; 4.3 vs 5.9%, Vet Dad*
 Age 20-24: 48 v 42%, Vet Mom ; 39 v 34%, Vet. Dad*

Father's Age:

↓ in GWV but breakdown not given (NS)

Araneta, M.R.G. et al Birth Defects Research 67: 246-260 2003. Prevalence of birth defects among infants of Gulf War veterans in Arkansas, Arizona, California, Georgia, Hawaii, and Iowa, 1989-1993

US birth defects

GWV mothers, vs NDV mothers: 450 vs 3966
 Less caucasian: 51 vs 60%; More often AA* (38 vs 31%)
 Less married: 72 vs 77%*
 Less completed high school: 45 vs 47%*
 Less active duty: 76 vs 88%*
 More Reserve or National Guard: 24 vs 12.4%*
 S1 less smoking mothers: 7.2 vs 8.9%, NS
 No dif or sl less alcohol, mothers: 1.4 vs 1.5%;
 8.9 vs 9.5% prenatal alcohol, born to male GWV vs NDV
 Fewer male births: 48.1 vs 50.1%, NS
 Fewer multiple births: 1.6 vs 2.5%, NS (young vs sick?)
 1.8 vs 2.4% for those born to male GWV *

*p < .05

Araneta, M.R.G. et al Birth Defects Research 67: 246-260 2003. Prevalence of birth defects among infants of Gulf War veterans in Arkansas, Arizona, California, Georgia, Hawaii, and Iowa, 1989-1993

US birth defects

Pre-war: 48 selected birth defects: No dif or trend toward fewer in GWV
 - GWV vs NDV females: 0.7% vs 2.3%, RR 0.31, NS
 - GWV vs NDV males: 1.56% vs 1.76%, RR 0.88, NS
 - None of a list of 48 were significantly different for males (despite mult comparisons). Estimates given for females only for the sole case where there was a defect in a GWV.

*p < .05

Araneta, M.R.G. et al Birth Defects Research 67: 246-260 2003. Prevalence of birth defects among infants of Gulf War veterans in Arkansas, Arizona, California, Georgia, Hawaii, and Iowa, 1989-1993

US birth defects

Postwar: 48 selected birth defects:
 - Females: hypospadias/epispadias 6.4 (1.5-26.8)
 - Males: 8 neg trend; 13 positive trend
 Males, Effects GWV vs NDV:
 Tricuspid insufficiency 2.7 (1.1-6.6) .039
 Aortic valve stenosis: 6.0 (1.2-31.0) .026
 Males, Effects GWV post- vs pre-deployment: (dif N)
 Aortic valve stenosis: 16.3(.09-294) .01? (5 vs 0)
 Renal agenesis or hypoplasia: 16.3 (.09-294), .01? (5 vs 0)
 Trend to fewer chromosomal anomalies: 0.2 (.03-1.6)
 Trend to fewer trisomy 13 specifically: 0.6 (.2-1.9)

None signif better than NDV; or than pre-war

*p < .05. Araneta, M.R.G. et al Birth Defects Research 67: 246-260 2003. Prevalence of birth defects among infants of Gulf War veterans in Arkansas, Arizona, California, Georgia, Hawaii, and Iowa, 1989-1993

US birth defects

Expect some differences by chance

Difficult to exclude chance as the source of these findings.

⁷p < .05

Araneta, M.R.G. et al. Birth Defects Research 67: 246-260 2003. Prevalence of birth defects among infants of Gulf War veterans in Arkansas, Arizona, California, Georgia, Hawaii, and Iowa, 1969-1993

Effects of Gestational Chlorpyrifos

Subjects: Pregnant rats exposed; offspring examined

Exposure: Oral chlorpyrifos in corn oil 0,3,5,7 mg/kg, gestation day 6 to 20. (3mg/kg ->10% CNS ChEi)*

- Low level ∇: below overt effects (moms or pups)

Outcomes: brain, heart, lung, serum ChE; brain ChAT; liver carboxylase activity. Postnatal day (pnd) 1,3,6,9,12 (sacrificed pups)

Brain ChE inhibition: 26-45%: persist to pnd 6; pnd 9 if hi-dose. (ChE starting to look ?>control by d 12, should look farther)

Liver carboxylesterase inhīb, dose dependent, recover with ChE

Nonspecific esterases equally inhibited by all doses.

Delayed reduction in ChAT: 1st noted pnd9, more signif pnd 12).

Rickardson et al 2003. J Toxicol Environ Health A 66:275-89. Effect of gestational exposure to chlorpyrifos on postnatal central and peripheral cholinergic neurochemistry

More on AChEi...

AChEi in animals, in many studies, leads to birth defects.

In some studies not.

May depend on agent, timing, duration exposure, and brain regions/outcomes examined

Considered to be “behavioral teratogens”