

**Posttraumatic Stress Disorder,
Military Sexual Trauma, and
Preterm Birth:
Evidence from 16,000 VA Pregnancies**

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**Posttraumatic Stress Disorder,
Military Sexual Trauma, and
Preterm Birth:
Evidence from 16,000 VA Pregnancies**

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Preface

Motivation and Explanation:

Perinatal/Neonatal Research in the VA

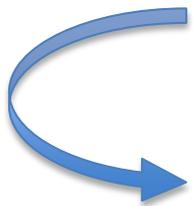
How, Where, Why?



Context

1. **Maternal stress and depression are increasingly recognized as potential risk factors for poor birth outcomes; The effect of posttraumatic stress is less studied.**
2. **As a growing number of reproductive-age females return from military service, the invisible wounds of war might impact pregnancy and thus the next generation.**

US conflicts in Afghanistan and Iraq



Change in demographics of military/veterans:
Women (reproductive age) increasingly represented

SPECIFIC AIM: Determine the extent to which posttraumatic stress is associated with spontaneous preterm birth.

HYPOTHESIS: Posttraumatic stress disorder (PTSD) contributes to preterm birth through direct biological effect and/or indirect behavioral risks.

Background: Preterm Delivery

- **Birth prior to 37wk gestation – prevalence 12%**
 - Spontaneous onset (ICD-9 644.2)
 - Medically indicated (risen in the past decade)
- **High Costs: Financial and emotional**
 - \$26 billion/yr Estimated Societal Cost (IOM)
 - \$52,000/premie (\$33,000 medical costs)
- **Despite prevalence, etiology poorly understood, poor at predicting**



Preterm Delivery – Risk Factors

- **Well established Risk Factors include:**
 - **Race** (US preterm rate 18% in blacks vs ≤ 10 whites)
 - **Age** (extremes)
 - **Low SES**
 - **Substance use**
 - **Medical Risks:** prior preterm, family hx, first pregnancy, infection, placental abnormalities, preeclampsia...

Challenge: disentangling demographic risk from the behavior risk factors and psychosocial stress/support/discrimination

- **Biology of Preterm Birth:**
 - **Neuroendocrine (Maternal-fetal HPA axis), Inflammatory, Vascular, and Behavioral pathways all implicated**

Stress ← ? → Preterm Delivery

“Stress” implicated, though role still unclear

e.g. Holzman et al 2009: pregnancy catecholamine levels → Preterm Birth

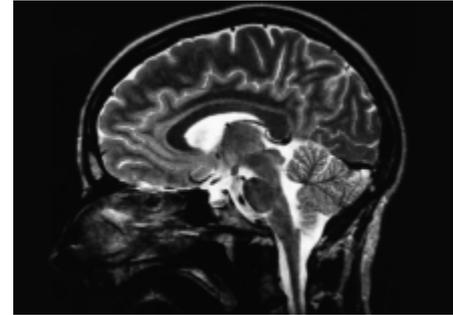
Class et al 2011: death in family during late 2nd trimester → Preterm, LBW

Multiple Pathways implicated in Preterm labor & delivery, through which stress could contribute:

- **Neuroendocrine (Maternal-fetal HPA axis),**
- **Inflammatory**
- **Vascular**
- **Behavioral**

Posttraumatic Stress Disorder

A mental health diagnosis,
with significant physiologic impact



Characterized by persistent distress or impaired function following a severely traumatic experience, with specific symptoms of:

- 1. Re-experiencing aspects of the trauma**
- 2. Numbness/Avoidance**
- 3. Hyper-arousal**

PTSD → Preterm Delivery ?

Hypothesis: Posttraumatic stress disorder contributes to preterm birth via direct biological effect and/or indirect behavioral risks.

Prior Studies Suggestive, but Limited and Inconsistent:

- Handful of small studies of PTSD post-trauma (9/11, Hurricane Katrina): underpowered inconsistent findings for Preterm and LBW
- Two medium size studies (Seng et al 2001 and 2011):
 - Cross-sectional, 455 PTSD+ pregnancies: OR 1.3 NON-Significant
 - Prospective, 255 PTSD+ pregnancies: correlation in sub-analysis, +PTSD/+Childhood Abuse → lower gestational age
- None to date within a Veteran population

PTSD → Preterm Delivery ?

VA presents an ideal setting to examine the association between PTSD and preterm birth.

National cohort of unprecedented size:

- **PTSD is particularly prevalent (13-21%) in women veterans.**
- **VA is largest integrated health system**
- **Female representation doubled in the post 9/11 era**

While military women experience diverse traumas, including combat, the most common antecedent of their PTSD is sexual trauma (often while in service)—the same is true for women in the general population.

METHODS

Retrospective cohort study

Cohort:

All deliveries covered (paid for) by VA 2000-12

Identified by algorithm of DRG, ICD-9 (Kuklina et al 2008)

N=16,334 deliveries (14,047 mothers)

– Maternal Data ONLY

– *future potential for infant data*

- policy change: VA covers first 7 days for newborn...
- Linking to State birth certificate data...

Data Sources



- **VA “Fee Basis files”** FY2000-FY2012
 - Reimbursed (non-VA facility) Delivery discharge data (DRGs, ICD-9)
- **VA Medical SAS Datasets** FY1997-FY2012
 - All VA encounters, diagnoses (Mental and medical), Demographics
- **“OEF/OIF/OND” Roster** Vets deployed to active operations:
 - Operation Enduring Freedom / Iraqi Freedom / New Dawn
(Afghanistan / Iraq)
- **Military Sexual Trauma Roster**
 - Results of near universal screening questions

Primary Outcome

Preterm Delivery: Defined by ICD-9-CM Code 644.2

“Onset (spontaneous) of delivery before 37 completed wks gestation.”

Limitations/Benefits:

1. Detects “spontaneous” only,
not “medically Indicated/ induced” preterm

Biased sample, but also arguably the sample of interest

Approximately 55% of PTB estimated to be spontaneous (Ananth et al 2006)

1. **Validated: ICD-9 for spontaneous preterm birth**

We validated ICD-9 code against California linked infant-maternal data:

- *Median gestational age 35 weeks (98% specific to <37wks)*
- *Likely under-codes for spontaneous (observed 40% vs. expected ~50% of preterm)*

Primary Predictor

Posttraumatic Stress Disorder: ICD-9-CM 309.81

- “PTSD” = 1 or more PTSD codes in VA encounters
ANYTIME prior to delivery (1997 -) (In or Outpatient)

Further distinguished diagnosis

- **“Active PTSD” = PTSD coded encounter within 365d**
prior to delivery hospitalization
 - *Rationale: Clinically relevant during prenatal period*
- **“Historical PTSD” = PTSD coded, but not within 365d**

Military Sexual Trauma (MST)

MST universal screening introduced 2002:

“While you were in the military . . .

- a) Did you receive uninvited and unwanted sexual attention, such as touching, cornering, pressure for sexual favors, or verbal remarks?;*
- b) Did someone ever use force or threat of force to have sexual contact with you against your will?”*

22% of all VA female patients screen positive

Covariates Considered in Primary Model

Demographics:

- Age
- Race (*missing 10%*)
- Marital Status

Obstetric:

- Twins/multiple gestations
- History of prior Cesarean

Potential exposures (*interaction terms also explored*) :

- “OEF/OIF” – Deployed to Iraq/Afghanistan Theatre
- MST Roster (*missing 5%*)

Potential Intermediaries / Explanatory Pathways Explored

- **Chronic Disease**
 - Hypertension, Asthma, Diabetes
 - *Conditions >2% prevalence in cohort and linked to preterm birth*
- **Substance Use:** Tobacco, Drug, ETOH diagnoses
 - VA encounters (365 days prior to delivery)
and/or
 - Prenatal period in Fee data
- **Mental Health:** Non-PTSD diagnoses (CCS categories)
captured as described for PTSD: ANYTIME prior / 365d prior

RESULTS

Selected Means

N = 16,334 Deliveries (2000-2012)

- **Overall Spontaneous Preterm Births: 7.8% (1,248)**
(similar to the 8% prevalence in National Inpatient Sample)
- **Deliveries with prior PTSD: 19% (3,049)**
with “Active PTSD” (dx within 365 days): 12% (1,921)
- **Positive to MST screening: 23% (3,568)**

Descriptive Bivariate Analysis

Patient Characteristics, by Posttraumatic Stress Disorder Status			
	All Deliveries (n=16,334)		P-value
	PTSD +	No PTSD	(chi-sq or T-Test)
Deliveries (%)	3,049 (19%)	13,285 (81%)	
Age (mean)	30.1	29.3	<0.001
Race			<0.001
White	70%	61%	
Black	20%	23%	
Deployed			
(Afghanistan/Iraq)	40%	28%	<0.001
MST positive	53%	16%	<0.001

Main Results: Unadjusted

Rate of Spontaneous Preterm Birth in Deliveries:

<u>PTSD Status</u>	<u>Rate</u>
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None:	7.4%
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Historical PTSD:	8.0%
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ACTIVE PTSD:	9.2%
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(p=.02)

Main Results: Multivariate Analysis

Adjusted for Demographics, Twins, Deployment History
(Total Deliveries=16,334 Preterm Delivery Events=1,248)

“Active PTSD” vs "Not Active" vs "No PTSD" as Predictor of Spontaneous Preterm Delivery					
Parameter			aOR	95% CI	P
No PTSD	no dx	n=13,285	1	Reference	
Active PTSD	dx within 365d	n=1,921	1.35	1.14 - 1.61	0.0007
Historical PTSD	last dx >365d	n=1,128	1.06	0.84 - 1.34	0.6

Analysis: Military Sexual Trauma

- MST itself was not at all a predictor of Preterm Birth
- But potential interaction with PTSD suggested when evaluated in the multivariate adjusted model :

No PTSD / No MST	(n=10,577)	reference
No PTSD / MST (+)	(n= 1,970)	0.96 (0.79 – 1.16)
Active PTSD(+) / MST (-)	(n= 797)	1.19 (0.89 – 1.58)
Active PTSD(+) / MST(+)	(n= 1,085)	1.43 (1.15 – 1.77)

Potential Explanatory Pathways

Those with PTSD show high comorbid Mental Health and Substance Use

Patient Characteristics, by Posttraumatic Stress Disorder Status

	PTSD (anytime prior)	No PTSD	P-value
Comorbid Medical			
Hypertension	8.5%	6%	<0.001
Diabetes	4%	3%	0.005
ASTHMA	11%	7%	<0.001
Comorbid Psych (anytime prior)			
Depression	80%	29%	<0.001
Drug Abuse	16%	4%	<0.001
Alcohol Abuse	18%	4%	<0.001

Potential Explanatory Pathways

Chronic disease – *predisposition in those with PTSD?*

Adjusting for Hypertension, Diabetes, Asthma:

- **no evidence of confounding**

Substance Abuse – *risky behaviors in causal pathway?*

Adjusting for active drug, alcohol, tobacco:

- Active PTSD only slightly attenuated, still significant
- **aOR 1.29 (1.08-1.55)**

Alternative MH Disorders

Alternative Mental Health Diagnoses – *very high rates of co-diagnoses:*

Adjusted for Depressive, Anxiety, Adjustment, Bipolar & Personality Disorders:

- **Robust, active PTSD aOR remains $\approx 1.30-1.33$**
- Nor were any of the alternative active MH disorders (more) significant predictors (only Bipolar disorder reached nominal significance 1.31 [1.00-1.75]).

Additional Sensitivity Analyses

Consistent results under various tests of model assumptions, e.g. :

- Stricter diagnostic definition for “confirmed” active PTSD (2+ occurrences of ICD-9)
- Restrict analysis to more recent years, when universal PTSD screening embedded in VA electronic record
- Adjusting for delivery count, delivery year, etc.

CONCLUSIONS

Conclusions

- **By far, largest cohort of PTSD exposed deliveries to be studied; 3000 with any PTSD history, and nearly 2000 with active PTSD. Largest previous study had about 450 women.**
- **Active PTSD appears to be risk factor for preterm birth, with increased risk of about 30-35%**
- **Suggests a subset, those with MST and active PTSD, with upwards of 40% increased risk**
- **Robust to adjustment for various potential confounders**

Discussion

Additional Strengths:

- **Validity of Predictor and Outcome**
- **Temporal relationship certain in design**
- **Unique opportunity to ask how distinct exposures (MST, Deployment) might alter the association, in large Veteran population**
 - MST+PTSD suggest (non-significant) worse outcomes
 - Deployment: no interaction with PTSD observed, but evidence of “healthy warrior effect” (lower risk pop.)

Discussion

Limitations:

- **Potential for Residual Confounding**

But reassuring: robustness to adjustment for known confounders; difference in affect for Active vs. Historical PTSD is reassuring

- **Lacked measure of severity of PTSD**

but Active vs. Historical difference may actually in part reflect a “dose effect”?

- **Generalizability?**

- *Not a phenomenon unique to combat: Majority of cohort were non-deployed*
- *PTSD Common in non-veteran population: ~5-10% of women → Obstetric providers will inevitably find themselves caring for women with active PTSD*

Implications

Our results suggest that:

- **Pregnant patients with active PTSD (a growing population in the VA) should be considered high risk pregnancies**
- **Maternal care coordination / pregnancy as opportunity for engaging patients in MH care**
- **Within VA: Consider Prenatal and Pre-conception care efforts specific to those with PTSD**

Future Research

Next steps for our research team:

- **Link VA-enrolled Veteran Parents to California birth certificate data:**
 - More robust birth outcome data (gestational age, etc)
 - Paternal PTSD contribution?
 - Compare to non-veteran cohort

Additional Research needed, e.g. ...

- **Treatment of PTSD modifies the risk for of preterm birth?**
- **PTSD as study population for biomarkers, stress hormones**
- **Treatment for Preventing Preterm Birth (17-OH Progesterone) for those with active PTSD?**

Exploratory Analyses of Other Birth Outcomes

	Crude Rates			Adjusted Model
	No PTSD	PTSD	p value	Active PTSD p value
Cesarean	33.5%	36.0%	0.02	NS
Gestational Diabetes	5.4%	7.5%	< .001	0.002*
Preeclampsia	4.6%	5.2%	0.05	0.02**
Hypertension in Preg. (not Preeclampsia)	5.9%	7.1%	0.03	NS
Intrauterine Growth Restriction	2.0%	2.5%	NS	NS
Fetal Abnormality	1.5%	1.8%	NS	0.05
Bleeding Complications	1.8%	1.3%	NS	NS
Fetal Demise	0.5%	0.6%	NS	NS
Chorioamnionitis	0.3%	0.3%	NS	NS

**In model also adjusted for pre-existing diabetes*

***In model also adjusted for pre-existing hypertension and tobacco use*

Consistent with potential endocrine/vascular/inflammatory alterations being the pathway by which PTSD affects pregnancy

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APPENDIX

Table 1. Characteristics of Deliveries Covered by the Veterans Administration (2000-2012), by PTSD Status

	Deliveries by PTSD Status, No. (%)						p-value
	Active Diagnosis (within 365 d) (n = 1921)		Historical Diagnosis (> 365 d) (n = 1128)		None (n = 13285)		
Spontaneous Preterm Birth	176	(9.2)	90	(8.0)	1072	(7.4)	0.02
Demographics							
Maternal Age, y							< .001
19-24	273	(14.2)	65	(5.8)	2290	(17.2)	
25-29	787	(41.0)	429	(38.0)	5257	(40.0)	
30-34	515	(26.8)	375	(33.2)	3689	(27.8)	
35-39	269	(14.0)	198	(17.6)	1614	(12.2)	
40-48	77	(4.0)	61	(5.4)	435	(3.3)	
Race							< .001
White	1344	(70.0)	776	(68.8)	8142	(61.3)	
African American or Black	371	(19.3)	243	(21.5)	3059	(23.0)	
Asian	26	(1.4)	11	(1.0)	219	(1.7)	
Native Hawaiian or Other Pacific Islander	36	(1.9)	9	(0.8)	142	(1.4)	
American Indian or Alaskan Native	20	(1.0)	8	(0.7)	102	(0.8)	
Missing or declined to answer	124	(6.5)	81	(7.2)	1575	(11.9)	
Married ^a	824	(43.2)	475	(43.0)	6187	(47.5)	< .001
Potential Trauma Exposure							
Military Sexual Trauma ^b	1085	(57.7)	513	(46.2)	1970	(15.7)	< .001
Deployed (OEF/OIF/OND)	863	(44.9)	361	(32.0)	3760	(28.3)	< .001
Obstetric History							
Twins/higher order gestation	41	(2.1)	31	(2.8)	276	(2.1)	0.3
Prior Cesarean	275	(14.3)	195	(17.3)	1847	(13.9)	0.007
Multiparous within VA cohort ^c	244	(12.7)	265	(23.5)	1791	(13.5)	< .001

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Spontaneous Preterm Birth	176	(9.2)	90	(8.0)	1072	(7.4)	0.02
Chronic Medical Conditions (within 3 years antepartum)							
Hypertension	169	(8.8)	91	(8.1)	835	(6.3)	< .001
Diabetes	90	(4.7)	36	(3.2)	414	(3.1)	0.002
Asthma	206	(10.7)	138	(12.3)	990	(7.5)	< .001
Substance Abuse/Dependence Diagnoses (within 1 year antepartum)							
Drug	217	(11.3)	50	(4.4)	387	(2.9)	< .001
Alcohol	165	(8.6)	26	(2.3)	175	(1.3)	< .001
Tobacco	351	(12.7)	143	(9.2)	1219	(10.5)	< .001
Active Mental Health Comorbidities (within 1 year antepartum)							
Depressive Disorder	1549	(80.6)	889	(78.8)	3813	(28.7)	< .001
Anxiety Disorder (other than PTSD)	552	(28.7)	148	(13.1)	1019	(7.7)	< .001
Adjustment Disorder	188	(9.8)	45	(4.0)	553	(4.1)	< .001
Bipolar Disorder	181	(9.4)	62	(5.5)	342	(2.6)	< .001
Personality Disorder	172	(9.0)	29	(2.6)	178	(1.3)	< .001