Male Fertility and Andrology Issues with Combat Genitourinary Trauma Warriors

Robert C. Dean, MD
COL, MC

Sexual Medicine Society of North America
AUA Meeting
San Diego, CA
7 May 2016
OBJECTIVES

• Explain the impact of fertility and hypogonadism in combat-related injuries especially in Genitourinary (GU) injuries

• Describe the medical and surgical treatments for infertility and hypogonadism in the combat injuries patients

• Describe the required funding changes, legal implications and training that will be required to manage the infertile family with combat-related GU injuries
Background

Mounted Attack from Improvised Explosive Devices (IED)
Improved survival ... with significant injuries
Blast and Shrapnel Wound to the Scrotum
Blast and Shrapnel Wound to the Scrotum
Blast and Shrapnel Wound to the Scrotum
Perineal Wound
Penile and Scrotum Skin Loss with Urethral Injury
GSW through the Cavernosal Bodies
GSW through the Corporal Bodies
Penile and Scrotal Loss
Complete penile and testis loss
This is the largest report of GU injuries during any military conflict.
The Joint Theater Trauma Registry was queried October 2001 and January 2008.

- 16,323 trauma admissions
- 819 had one or more GU injuries.
- 65% were because of explosions
- The average casualty age was 26 years (range, 18–58 years)

*J Trauma. 2010;69: S175–S178*
Epidemiology of Genitourinary Injuries

Distribution of GU injuries

<table>
<thead>
<tr>
<th>GU Injury Location</th>
<th># of Injuries</th>
</tr>
</thead>
<tbody>
<tr>
<td>Scrotum</td>
<td>257</td>
</tr>
<tr>
<td>Kidney</td>
<td>203</td>
</tr>
<tr>
<td>Bladder</td>
<td>189</td>
</tr>
<tr>
<td>Penis</td>
<td>126</td>
</tr>
<tr>
<td>Testicle</td>
<td>97</td>
</tr>
<tr>
<td>Ureter</td>
<td>24</td>
</tr>
<tr>
<td>Urethra</td>
<td>7</td>
</tr>
</tbody>
</table>

J Trauma. 2010;69: S175–S178
# Epidemiology of Genitourinary Injuries

<table>
<thead>
<tr>
<th>Location of Injury</th>
<th>Current Conflict</th>
<th>Baghdad CSH²</th>
<th>Bosnia and Croatia¹⁰</th>
<th>Vietnam¹¹</th>
<th>World War II⁹</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kidney</td>
<td>22.9</td>
<td>29.6</td>
<td>39.6</td>
<td>19.1</td>
<td>40</td>
</tr>
<tr>
<td>Ureter</td>
<td>2.7</td>
<td>2.0</td>
<td>7.8</td>
<td>5.2</td>
<td>3.3</td>
</tr>
<tr>
<td>Bladder</td>
<td>21.3</td>
<td>13.3</td>
<td>17.2</td>
<td>10.4</td>
<td>11.6</td>
</tr>
<tr>
<td>Urethra</td>
<td>0.8</td>
<td>17.3</td>
<td>4.6</td>
<td>12.0</td>
<td>15</td>
</tr>
<tr>
<td>Scrotum</td>
<td>29.0</td>
<td>19.4</td>
<td>22.7</td>
<td>32.8</td>
<td>30</td>
</tr>
<tr>
<td>Testicle</td>
<td>9.1</td>
<td>12.2</td>
<td>*</td>
<td>*</td>
<td>†</td>
</tr>
<tr>
<td>Penis</td>
<td>14.2</td>
<td>6.1</td>
<td>8.1</td>
<td>18.5</td>
<td>†</td>
</tr>
</tbody>
</table>

* Testicular trauma is categorized as scrotal trauma in these studies.
† Testicular and penis trauma is categorized as scrotal trauma in this study.
## Epidemiology of Genitourinary Injuries

### Table 1. Comparison of GU Injuries in the Current Conflict to Previous Conflicts as a Percentage of Total Injuries

<table>
<thead>
<tr>
<th>Location of Injury</th>
<th>Current Conflict</th>
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<td>12.2</td>
<td>*</td>
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<td>*</td>
</tr>
<tr>
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<td>6.1</td>
<td>8.1</td>
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<td>*</td>
</tr>
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† Testicular and penis trauma is categorized as scrotal trauma in this study.
Epidemiology of Genitourinary Injuries

ONCOLOGY/RECONSTRUCTION
ORIGINAL ARTICLE

Urethral and penile war injuries: The experience from civil violence in Iraq

Issam S. Al-Azzawi a, Mamdouh M. Koraitim b, c

a Department of Urology, Al-Mustansiriya College of Medicine, Baghdad, Iraq
b College of Medicine, University of Alexandria, Egypt

c Al-Yarmouk Hospital, Baghdad
Jan 2004 to Jun 2008
2800 causalities with 504 (18%) having Genitourinary Trauma
64% Civilian
36% Iraqi Military
Most common cause of Injury – IED (56%)
Figure 14. Total number of GU injuries among all admissions from OIF/OEF from 2005 to 2010. Source JTTR.
Figure 13. Rate of GU injury among all admissions from OIF/OEF from 2005 to 2010. Historical average is 2-5%. Source JTTR.
TESTOSTERONE SUPPLEMENTATION
Genital Injury – Testosterone Replacement

• Several Studies (animal and human) have demonstrated near castrate levels of Testosterone occur following trauma.

• Cernak noted the Testosterone levels continue to fall for 5 days following admission for trauma.
  – Patients were only followed for 5 days
  – No description of the injuries were described

Genital Injury – Testosterone Replacement
When to Start?

• Acute administration of Supplementation
  – Jeschke et al, used a testosterone analog (oxandrolone) acutely in burn patients
    – decrease in protein loss and wasting
    – shorter hospital stays.

• Delay treatment of Testosterone
  – Gee et al, noted at a level I Trauma Center patients with higher Testosterone levels
    – Higher chance to develop Acute Respiratory Distress Syndrome
  – Park et al, in a mouse model found low testosterone
    – Protective for renal ischemic trauma
  – Anathakrishnan et al, in an rat model found that testosterone
    – Potentiated lung and gut injury in hemorrhagic and burn trauma

Genital Injury – Testosterone Replacement
WRNMMC Pattern of Care

• Testosterone Levels at arrival and monthly to follow the trend in recovery

• For Elevating Testosterone – Observation
• For Low Testosterone – treatment at the start of Physical Therapy

• Review of the cases under IRB approval from 2001 to 2011
• Both conflicts (OIF and OEF)
• Surgery records were reviewed for extent of GU injury

J Urol., Vol 193 618-622, Feb 2015
Testosterone Recovery after Polytrauma and Scrotal Injury in Patients from Operation Enduring Freedom and Operation Iraqi Freedom

Molly Williams,* Inger Rosner, Yongmei Chen, Jennifer Cullen,† James Jezior and Robert Dean‡

From the Center for Prostate Disease Research, Walter Reed National Military Medical Center, Bethesda, Maryland

- 55 Patients with evaluable information
- 51 Patients from Operation Enduring Freedom
- 4 Patients for Operation Iraqi Freedom
- Most trauma was from IED Blast Injury
Genital Injury – Testosterone Replacement

• 55 Trauma Patients -- Groups
  – Scrotal Exploration /No testicle tissue loss
  – Scrotal Injury with Testicle loss
  
  – Bilateral Testicular Loss (omitted from data analysis)
## Description of Patients

<table>
<thead>
<tr>
<th>Variable</th>
<th>Overall</th>
<th>Scrotal injury without testicular loss</th>
<th>Scrotal injury with testicular loss*</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>N</td>
<td>55</td>
<td>30</td>
<td>25</td>
<td>0.5052</td>
</tr>
<tr>
<td>Age (yr)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean (SD)</td>
<td>24.2(3.9)</td>
<td>24.0 (4.2)</td>
<td>24.5 (3.6)</td>
<td></td>
</tr>
<tr>
<td>Median (range)</td>
<td>23 (19-38)</td>
<td>22 (19-38)</td>
<td>25 (20-30)</td>
<td></td>
</tr>
<tr>
<td>Baseline T</td>
<td></td>
<td></td>
<td></td>
<td>0.0901</td>
</tr>
<tr>
<td>Mean (SD)</td>
<td>49.1 (76.3)</td>
<td>63.7 (84.3)</td>
<td>31.7 (62.6)</td>
<td></td>
</tr>
<tr>
<td>Median (range)</td>
<td>18 (0-353)</td>
<td>29.7 (0-353)</td>
<td>12.2 (0-260.4)</td>
<td></td>
</tr>
<tr>
<td>Testosterone velocity (ng/dL/day)*</td>
<td></td>
<td></td>
<td></td>
<td>0.2015</td>
</tr>
<tr>
<td>Mean (SD)</td>
<td>2.4 (5.0)</td>
<td>2.7 (5.3)</td>
<td>1.9 (4.8)</td>
<td></td>
</tr>
<tr>
<td>Median (range)</td>
<td>0.62 (-3.1-20.6)</td>
<td>0.80 (-1.3-20.6)</td>
<td>0.23 (-3.1-18.7)</td>
<td></td>
</tr>
<tr>
<td>Time to replacement (day)**</td>
<td></td>
<td></td>
<td></td>
<td>0.5233</td>
</tr>
<tr>
<td>Mean (SD)</td>
<td>158.3 (161.7)</td>
<td>161.5 (133.4)</td>
<td>154.5 (193.1)</td>
<td></td>
</tr>
<tr>
<td>Median (range)</td>
<td>87 (21-662)</td>
<td>109 (21-479)</td>
<td>70 (26-662)</td>
<td></td>
</tr>
<tr>
<td>T replacement</td>
<td></td>
<td></td>
<td></td>
<td>0.0176</td>
</tr>
<tr>
<td>Non-replacement</td>
<td>25</td>
<td>18 (60.0)</td>
<td>7 (28.0)</td>
<td></td>
</tr>
<tr>
<td>Replacement</td>
<td>30</td>
<td>12 (40.0)</td>
<td>18 (72.0)</td>
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</tr>
</tbody>
</table>
## Predictors of Testosterone Placement

<table>
<thead>
<tr>
<th>Variable</th>
<th>No-replacement</th>
<th>Replacement</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>N</td>
<td>25</td>
<td>30</td>
<td></td>
</tr>
<tr>
<td>Age (yr)</td>
<td></td>
<td></td>
<td>0.5660</td>
</tr>
<tr>
<td>Mean (SD)</td>
<td>23.6 (3.0)</td>
<td>24.8 (4.6)</td>
<td></td>
</tr>
<tr>
<td>Median (range)</td>
<td>23 (19-30)</td>
<td>24.5 (19-38)</td>
<td></td>
</tr>
<tr>
<td>Baseline T</td>
<td></td>
<td></td>
<td>0.0063</td>
</tr>
<tr>
<td>Mean (SD)</td>
<td>77.5 (93.2)</td>
<td>25.5 (48.7)</td>
<td></td>
</tr>
<tr>
<td>Median (range)</td>
<td>35.2 (0-353)</td>
<td>11.9 (0-260.4)</td>
<td></td>
</tr>
<tr>
<td>Testosterone velocity (ng/dL/day)</td>
<td>&lt;.0001</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean (SD)</td>
<td>5.2 (6.4)</td>
<td>-0.04 (0.96)</td>
<td></td>
</tr>
<tr>
<td>Median (range)</td>
<td>1.9 (-0.3-20.6)</td>
<td>0.1 (-3.1-1.5)</td>
<td></td>
</tr>
</tbody>
</table>

- Average time to achieve Testosterone Recovery – 4.5 months
Testosterone Replacement for GU Trauma

Conclusions

1) Virtually all trauma patients development low testosterone levels

2) Testosterone Supplementation should be delayed until patients are removed from the critical care setting

3) Patients with scrotal injuries with testicular tissue loss are more likely to need Testosterone Supplementation

4) Predictors for endogenous testosterone recovery are:
   1) Higher Initial Testosterone Levels upon admission
   2) Positive Testosterone Velocity

5) Average Time for Testosterone Recovery is 4.5 months
Reminder of important clinical lesson

CASE REPORT

Traumatic andropause after combat injury

Gareth Huw Jones, ¹ Jackson Kirkman-Brown, ² Davendra Murray Sharma, ³ Douglas Bowley ⁴

BODY ARMOR FOR THE PELVIS
Pelvic Protective Undergarment (PPU)

Silk Base

Kevlar woven fibers

Protects the Genitalia and Femoral Vessels

Comfortable

2 Tiers (outer garment and inner garment)
Pelvic Protective Over Garment (POG)

**Tier 1**
A Protective Under Garment (PUG) worn next to the skin which is designed to reduce penetrations of dirt and fine debris.

- **Crye Precision Protective Under Garment** (Note - available in light and medium weight)
- **Cooneen, Watts & Stone (CWS) Protective Under Garment**
- **K-L Manufacturing Protective Under Garment**

**Tier 2**
A Protective Over Garment (POG) worn over the ACU Pant which is designed to reduce penetrations of fragmenting munitions and larger debris.

- **Crye Precision Contoured Groin Wrap**
- **Shock Doctor Female Pelvic Protector** (Note - worn with jock strap or female jock shorts)
- **Shock Doctor Titan Alloy** (Note - worn with jock strap)
- **Hawk Protection Groin Wrap**

Shock Doctor protectors are worn in conjunction with Tier 1 PUGs.
Pelvic Protective Undergarment (PPU)

• Research compiled by the Operations Research and Systems Analysis Division of Combined Joint Task Force

• 45,000 Units Delivered between Feb. 1, 2010, and Feb. 28, 2011

• Admissions to Combat Support Hospital

• 61 warfighters (control group)
  – Did not wear the PPS and suffered one or more lower extremities amputation from dismounted IED blast

• 63 warfighters (experimental group)
  – Confirmed wearing the PPS and suffered one or more lower extremities amputation from dismounted IED blast
<table>
<thead>
<tr>
<th></th>
<th>Warfighters with Extremity Injuries</th>
<th>Scrotal Injury</th>
<th>Testicular Rupture</th>
</tr>
</thead>
<tbody>
<tr>
<td>Non wearers of PPU</td>
<td>61</td>
<td>34 (56%)</td>
<td>13 (21%)</td>
</tr>
<tr>
<td>Wearers of PPU</td>
<td>63</td>
<td>21 (33%)</td>
<td>2 (3%)</td>
</tr>
</tbody>
</table>
FERTILITY ISSUES FOR COMBAT TRAUMA PATIENTS
• 20 year old
• Enlisted Ordinance Removal Specialist, US Navy
• Four extremities amputations
• Complete bilateral testicular loss
• Perineal injuries
• Penile injuries

• DOI: 3 May 2012
• Date of Arrival: 6 May 2012
Fertility

• Shefi et al, (Human Repro 2006), Posthumous sperm retrieval should occur within 36 hrs; however, perimortem collection varies widely.
• Jarrow et al, (J Urol, 1996), viable sperm can be found in the seminal vesicle 5 days following ejaculation

• Date of Seminal Vesicle Sperm Harvest: 9 May 2012
  – (6 days following injury date)
• Our patient underwent Seminal Vesicle Aspiration
  – 560,000 sperm retrieved
  – Motility noted with Pentoxifylline

Tissue Care
Seminal Vesicle Harvest
Case Series

• Six wounded warriors
• Walter Reed National Military Medical Center, Bethesda, Maryland
• Ages 23-41
• Operation Enduring Freedom

May 2012-Jan 2014
<table>
<thead>
<tr>
<th>Pt</th>
<th>Age</th>
<th>Interval from Injury to Retrieval</th>
<th>BKA</th>
<th>Pelvic/Perineal Fractures</th>
<th>Penile Injury</th>
<th>Scrotal Injury</th>
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<tbody>
<tr>
<td>1</td>
<td>41</td>
<td>11 days</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>2</td>
<td>23</td>
<td>7 days</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>3</td>
<td>23</td>
<td>6 days</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>4</td>
<td>27</td>
<td>12 days</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>5</td>
<td>31</td>
<td>9 days</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>6</td>
<td>27</td>
<td>5 days</td>
<td></td>
<td>X</td>
<td>X</td>
<td>X</td>
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</table>
## Surgical Outcomes

<table>
<thead>
<tr>
<th>Pt</th>
<th>Age</th>
<th>Interval from Injury to Retrieval</th>
<th>Volume</th>
<th>Motility</th>
<th>Concentration</th>
<th>TMS</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>41</td>
<td>11 days</td>
<td>0.5mL</td>
<td>0%</td>
<td>100K</td>
<td>0</td>
</tr>
<tr>
<td>2</td>
<td>23</td>
<td>7 days</td>
<td>1.8mL</td>
<td>0%</td>
<td>600K</td>
<td>0</td>
</tr>
<tr>
<td>3</td>
<td>23</td>
<td>6 days</td>
<td>1.7mL</td>
<td>5%</td>
<td>6.4M</td>
<td>500K</td>
</tr>
<tr>
<td>4</td>
<td>27</td>
<td>12 days</td>
<td>1.1mL</td>
<td>0%</td>
<td>2.2M</td>
<td>0</td>
</tr>
<tr>
<td>5</td>
<td>31</td>
<td>9 days</td>
<td>0.45mL</td>
<td>0%</td>
<td>100K</td>
<td>0</td>
</tr>
<tr>
<td>6</td>
<td>27</td>
<td>5 days</td>
<td>0.4mL</td>
<td>&lt;1%</td>
<td>40K</td>
<td>&lt;1K</td>
</tr>
</tbody>
</table>
Patient 5

Pre-Cryo: Volume: 0.45mL, Motility: 0%, Concentration: 100K

WRNMMC IVF Jan 2013

13 oocytes underwent ICSI

5 oocytes fertilized

Day 3: Grade V Embryos → Embryo transfer with negative pregnancy test
Patient 6

Pre-Cryo

- Volume 0.4mL, TMS <1K = Three vials cryopreserved

Cycle 1 IVF Aug2014

- 9 oocytes underwent ICSI
- 4 oocytes fertilized

Day 5

- Expanded Blastocyst B/B → Transferred with negative pregnancy test
- No frozen embryos
Patient 6

Cycle 2 IVF Jan2015
- 17 oocytes underwent ICSI
- 8 oocytes fertilized

Day 5/6
- 6 embryos arrested
- Expanded Blastocyst B/B on Day 5
- Expanded Blastocyst B/B on Day 6

Freeze
- No transfer due to Ovarian Hyperstimulation Syndrome Risk
- 2 embryos frozen
Cycle 3 IVF FET
Cycle: July 2015
1 embryo transferred
+ Pregnancy Test
+ Live Birth

Patient 6
Seminal Vesicle Sperm Aspiration from Wounded Warriors: A Case Series

Authors
Mae Wu Healy, D.O. a, b
Belinda J. Yauger, M.D. a, b
Aidita N James, Ph.D. c
Robert C. Dean, M.D. d

Institutional Affiliations
a Department of Obstetrics and Gynecology, Division of Reproductive Endocrinology and Infertility, Walter Reed National Military Medical Center, Bethesda, Maryland
b Program in Reproductive and Adult Endocrinology, Eunice Kennedy Shriver National Institute of Child Health and Human Development, National Institutes of Health, Bethesda, Maryland
c A.R.T. Institute of Washington Inc., Walter Reed National Military Medical Center, Bethesda, Maryland
d Department of Urology, Division of Andrology, Walter Reed National Military Medical Center, Bethesda, Maryland

Six patients are presented with lower extremity, pelvic, and perineal injuries resulting from dismounted IEDs in theater. They underwent seminal vesicle sperm retrievals within 5-12 days of the initial injury. Sperm retrieved were analyzed and cryopreserved. Two patients subsequently attempted IVF/ICSI with fertilization documented. Currently, there have been one pregnancy and one live birth.
MEMORANDUM FOR ASSISTANT SECRETARY OF THE ARMY (MANPOWER AND RESERVE AFFAIRS)
ASSISTANT SECRETARY OF THE NAVY (MANPOWER AND RESERVE AFFAIRS)
ASSISTANT SECRETARY OF THE AIR FORCE (MANPOWER AND RESERVE AFFAIRS)
DIRECTOR, JOINT STAFF
DEPUTY DIRECTOR, TRICARE MANAGEMENT ACTIVITY
COMMANDER, JOINT TASK FORCE NATIONAL CAPITAL REGION MEDICAL

SUBJECT: Policy for Provision of In Vitro Fertilization Services for the Benefit of Seriously Injured Service Members

The Department is committed to ensuring the maximum support for our members who have become seriously injured as a result of their service on Active Duty. Although many medical and other benefits are available to these members and their families, members with spinal and other injuries that make it impossible to conceive a child naturally are not provided TRICARE coverage, which can assist them in becoming a parent. Under references (a) and (c), Active Duty Service members receive a wide variety of services that are not covered under the TRICARE basic program and include benefits similar to those provided under reference (b) to Active Duty family members who have a serious physical disability or an extraordinary physical or psychological condition.

Reference (b) benefits, generally referred to as TRICARE extended care health option benefits, include services to assist in the reduction of the disabling effects of a qualifying condition. For those members who are medically retired from the Armed Forces due to a serious illness or injury, reference (d) authorizes the Department to provide the retired member the same medical care as an Active Duty Service member when the care is not reasonably available to such retired members in the Department of Veteran Affairs. Medical care for medically retired members under reference (d) is scheduled to terminate December 31, 2012. The intent of this policy is to utilize the above authorities to provide a quality of life benefit and to assist in reduction of the disabling effects of his qualifying condition.

Attachments: As stated

CC: Surgeon General of the Army
Surgeon General of the Navy
Surgeon General of the Air Force
Joint Staff Surgeon
Funding for IVF for Combat Warriors

- Wounded Warrior must be on active duty
- Patient must be legally married
- Wound from Combat must have caused Infertility
- Wounded Warrior must be Seriously or Severely Ill/Injured (Category II or III)
- Memorandum and Checklist must be submitted to the individual services for approval every 2 months
Immediate surgical management of combat-related injury to the external genitalia

Davendra M Sharma,¹ D M Bowley²

TESTICULAR INJURY
The optimal management of blast injury of the testes is as yet undefined. The objectives are three-fold: to preserve spermatogenesis and testosterone production and to restore the aesthetic appearance of the external genitalia. There are three options for the immediate management of testicular injury - testicular conservation, orchidectomy and early sperm retrieval. These are not mutually exclusive and the choice of surgical management is governed by several factors including the extent of injury and the logistics and expertise available. *Early sperm retrieval is the first choice recommendation for casualties with severe testicular injury entering the UK evacuation chain.*

A content analysis of posthumous sperm procurement protocols with considerations for developing an institutional policy

Sarah M. Bahm, M.D., Katrina Karkazis, Ph.D., M.P.H., and David Magnus, Ph.D.
Stanford Center for Biomedical Ethics, Stanford University, Stanford, California

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Sperm Harvest – Legal and Ethical Concerns

• American Society of Reproductive Medicine
  – The request to harvest sperm without prior known consent of the patient need NOT be honored.

• Universal Anatomic Gift Act of 2006
  – Allows next of kin to consent to the retrieval of organs and tissues unless there is evidence the deceased would not have consented.

• Ruling in 2006
  – Under the Gift Act of 2006 -- the anatomical gift, including the gift of sperm, by the donor or, if the donor did not refuse to make the gift, by the donor’s parents following the donor’s death

• Review of 8 Protocols of Posthumous Sperm in the USA reveals large variations in patterns of care
Sperm Harvest – Legal and Ethical Concerns

• Is there consent? And from which party involved?
• Does the patient want to be a father?
  – Fatherhood after death
  – Fatherhood after injury
  – Fatherhood out of wedlock
• Is sperm property?
• Is there undue burden on the spouse to have the patient’s child?

• For women should oocytes be harvested?
  – Selection of segregate for pregnancy?
Conclusions

• IED related lower extremity, perineal, genital, and scrotal trauma require extensive involvement by urology.

• Advanced Field Medicine has Increased Survival

• Trends in Urological Care is Evolving

• Developing an understanding of sexual, social, and reproductive outcomes is essential to providing the best care to these patients
Thank You
QUESTIONS