Lifestyle and aneuploidy: Is there a correlation?

Helen Tempest
htempest@fiu.edu

FIU | Herbert Wertheim College of Medicine

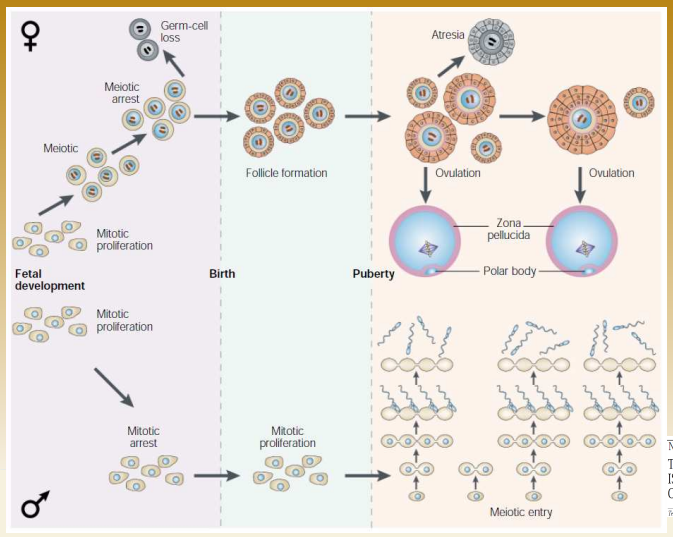
Chromosome aneuploidy

- Hallmark of human reproduction
- Leading cause:
  - Pregnancy loss
    - ~60-80% of conceptions
    - ~4% clinically recognized pregnancy
  - Mental impairment
  - Developmental disabilities

Parental origin of aneuploidy

	Paternal (%)	Maternal (%)
Trisomy 13	15	85
Trisomy 18	10	90
Trisomy 21	5	95
45,X	80	20
47,XXX	5	95
47,XXY	45	55
47,XYY	100	0

Sex-specific meiotic timelines



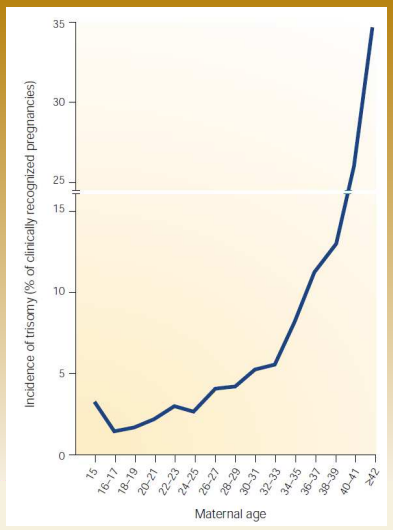
NATURE REVIEWS | GENETICS

TO ERR (MEIOTICALLY) IS HUMAN: THE GENESIS OF HUMAN ANEUPLOIDY

Risk factors for aneuploidy

- Advancing age
- Karyotype aberrations
- Lifestyle (diet/exercise)
  - Alcohol/drug use/smoking/caffeine
- Environmental/occupational exposures:
  - Air pollution, BPA, phthalates, benzene, pyrethroids
  - Infections
- Therapeutic exposures:
  - Chemotherapy/radiation

Advanced maternal age



NATURE REVIEWS | GENETICS

TO ERR (MEIOTICALLY) IS HUMAN: THE GENESIS OF HUMAN ANEUPLOIDY

Terry Hassold and Patricia Hunt

Lifestyle/environmental influence on oocyte aneuploidy

- Humans: link has been difficult to establish
  - Importance of maternal age
  - Separation in time: sensitive window (fetal) & nondisjunction
  - Heterogeneity in nondisjunction
- Mice: bisphenol A (BPA) exposure increased aneuploidy
  - Study could not be replicated
  - Complex interaction between diet on BPA aneugenic potential
    - Phytoestrogens in feed varied between batches
  - If exposed during fetal life, higher rates of aneuploidy


SCIENTIFIC AMERICAN

HEALTH

Just How Harmful Are Bisphenol A Plastics?

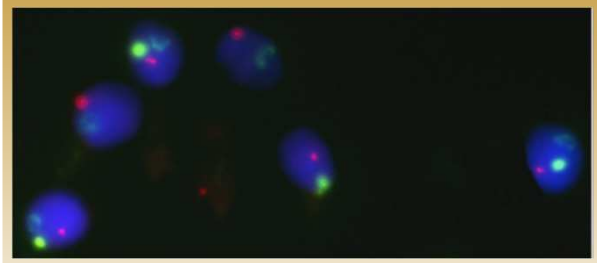
Patricia Hunt, who helped to bring the issue to light a decade ago, is still trying to sort it all out

Risk factors for sperm aneuploidy

- Advancing paternal age ?
- Infertility/karyotype aberrations
- Lifestyle (diet/exercise)
  - Alcohol/drug use/smoking/caffeine
- Environmental/occupational exposures:
  - Air pollution, BPA, phthalates, benzene, pyrethroids
  - Infections
- Therapeutic exposures:
  - Chemotherapy/radiation

Sperm aneuploidy

- All men have a proportion of aneuploid sperm (2-4%)
- > 50 published studies



- More frequent for chromosomes 21, 22, X & Y

Are sperm aneuploidy levels variable?

- 10 normal men – (340,534 sperm)
  - Sperm aneuploidy levels over 2 year period
    - 6 month intervals
  - Baseline remarkably constant
  - Stable variants consistently produce higher frequencies
  - Sporadic events significant increase or decrease in aneuploidy frequencies at a single time point
    - "life event" can exert an effect on sperm aneuploidy

Intra-individual and inter-individual variations in sperm aneuploidy frequencies in normal men

Helen G. Tempest, Ph.D.,[a] Evelyn Ko, B.Sc.,[a] Alfred Rademaker, Ph.D.,[b] Peter Chan, M.D.,[c] Bernard Robaire, Ph.D.,[d] and Renée H. Martin, Ph.D.[a]

0015-0282/09/$36.00
doi:10.1016/j.fertnstert.2007.11.002
Fertility and Sterility® Vol. 91, No. 1, January 2009 165

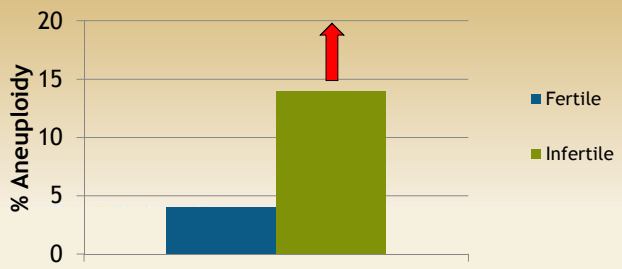
Karyotype aberrations & sperm aneuploidy

- Frequency of unbalanced gametes reported varies:
  - Robertsonian translocations: 3-36%
  - Reciprocal translocations: 29-81%
  - Inversions: 1-54%
- PGD ESHRE consortium data collection X
  - 3,652 embryos: 74% unbalanced; 26% normal/balanced
- 47,XXY & 47,XYY males: 0-25%

Tempest HG (2011) Syst Biol Reprod Med 57:93-101; Ferlin A et al (2005) Cytogenet Genome Res 111:310-316; Sarrate Z (2005) AJA 7:227-236; Data Collection X (2010) Hum Reprod 25:2685-2707

Male infertility & aneuploidy

- Infertile men ~3x increase
- Aneuploidy increases with severity of the infertility phenotype



Lifestyle, environmental & therapeutic exposure studies

- Generally small sample sizes
- Comparisons between studies are problematic:
  - Age
  - Heterogeneity (subjects & study design)
  - Duration & length of exposure
  - Self-reported vs. measured exposures
  - Compounding effects that are near impossible to separate:
    - Lifestyle & occupation
    - Susceptibility
    - Metabolism
    - Interactions
    - Transient vs. fixed

Lifestyle exposures

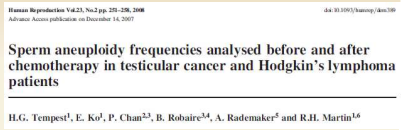
- Smoking
  - Disomy: 3 (2x) 13 (3x); XX (1.5x); YY (2x); XY (2x)
    (Pereira et al 2014; Shi et al 2001; Robbins et al 1997; Rubes et al 1998; Naccarati et al 2003)
- Alcohol: Disomy XY (1.38x); XX (linear increase)
  (Robbins et al 2005; Robbins et al 1997)
- Folate, zinc & antioxidants: Folate disomy XX (-0.75x)
  (Young et al 2008)
- Large study (n=212) associations with:
  - Coffee: Disomy 18; Tight underwear: Disomy 18 & nullisomy 13; Obesity: Disomy 21; Cell phone usage >11 yr: Disomy X & Y
    (Jurewicz et al 2014)

Environmental & occupational exposures

- Agents:
  - Pyrethroids (e.g., CDCCA, TDCCA, 3BPA)
  - Phthalate (e.g., DEHP, DEP, DBP)
  - Benzene
  - Air pollution
  - Polycyclic aromatic hydrocarbons (e.g., 1-OHP)
  - Organochlorines (e.g., PCBs, p,p'-DDE)
- Most studies report significant increases (<3x)

Chemotherapy exposure

- Testicular cancer & Hodgkin lymphoma patients
- Pretreatment aneuploidy levels significantly higher
  - Presence of cancer alone increased sperm aneuploidy
- Chemotherapy increased sperm aneuploidy levels
- Levels return to fertile range 18-24 months later
- Greater susceptibility of meiotic vs. premeiotic cells



Human Reproduction Vol.23, No.2 pp. 251–258, 2008
Advance Access publication on December 14, 2007

Sperm aneuploidy frequencies analysed before and after chemotherapy in testicular cancer and Hodgkin's lymphoma patients

H.G. Tempest[1], E. Ko[1], P. Chan[2,3], B. Robaire[3,4], A. Rademaker[5] and R.H. Martin[1,6]

Emerging picture (for males)

- Almost all studies have identified significant increases in aneuploidy correlated with all investigated exposures
- Moderate increases
  - 1 – 3x higher
  - Not a globally increased & not always the same error
- Exposures are often transient
  - Sperm aneuploidy levels therefore will likely fluctuate

Blackwell Publishing

Complementary Medicine

Significant reduction of sperm disomy in six men: effect of traditional Chinese medicine?

Helen G. Tempest, Sheryl T. Homa, Xiao-Ping Zhai, Darren K. Griffin

AJA

Intra-individual and inter-individual variations in sperm aneuploidy frequencies in normal men

Helen G. Tempest, Ph.D.,[a] Evelyn Ko, B.Sc.,[a] Alfred Rademaker, Ph.D.,[b] Peter Chan, M.D.,[c] Bernard Robaire, Ph.D.,[d] and Renée H. Martin, Ph.D.[a]

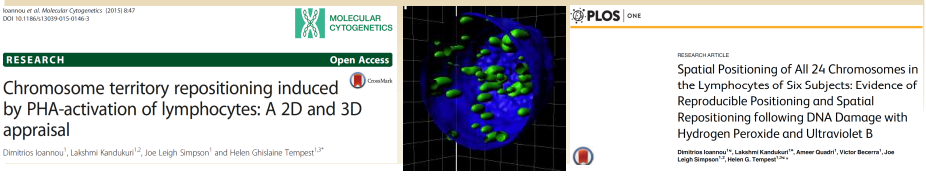
0015-0282/09/$36.00
doi:10.1016/j.fertnstert.2007.11.002

Fertility and Sterility® Vol. 91, No. 1, January 2009 185

Copyright ©2009 American Society for Reproductive Medicine, Published by Elsevier Inc.

Can epigenetic alterations induce aneuploidy?

- Exposures shown to affect DNA methylation, genomic stability, posttranslational histone modifications
  - Could contribute to the generation of aneuploidy
- "Silent" sperm cell carries unique epigenetic markings
  - Delivers "poised" set of developmental genes to the embryo
- Chromatin organization perturbations?
  - Could affect chromosome pairing & delivery of "poised" genes



Ioannou et al. Molecular Cytogenetics (2015) 8:47
DOI 10.1186/s13039-015-0146-3

MOLECULAR CYTOGENETICS

RESEARCH Open Access

Chromosome territory repositioning induced by PHA-activation of lymphocytes: A 2D and 3D appraisal

Dimitrios Ioannou[1], Lakshmi Kandukuri[1,2], Joe Leigh Simpson[1] and Helen Ghislaine Tempest[1,3*]

PLOS ONE

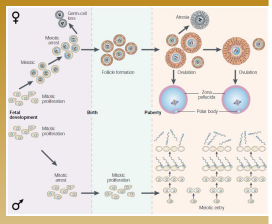
RESEARCH ARTICLE

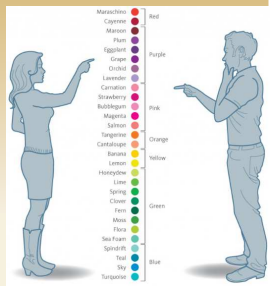
Spatial Positioning of All 24 Chromosomes in the Lymphocytes of Six Subjects: Evidence of Reproducible Positioning and Spatial Repositioning following DNA Damage with Hydrogen Peroxide and Ultraviolet B

Dimitrios Ioannou[1]*, Lakshmi Kandukuri[1]*, Ameer Quadri[1], Victor Becerra[1], Joe Leigh Simpson[1,2], Helen G. Tempest[1,2]*

Conclusions

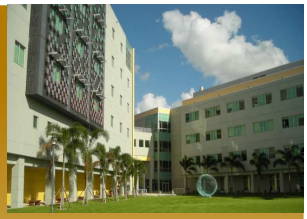
- Association NOT causation
  - Mechanism of action?
- Are increased sperm aneuploidy levels clinically significant?
  - Transient vs. fixed?
- Significant differences between males & females
  - Temporal differences in meiosis
  - Timing of exposure
- Genetic differences (mRNA, spindle function, cohesins) susceptibility?

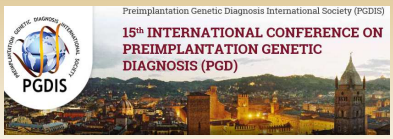




Acknowledgements

Dimitrios Ioannou Ph.D.
Lakshmi Rao Ph.D.
Brittany-Lee Roberts
Nicole Millan
Elizabeth Jordan
Amanda Vaccarella
Ameer Quadri
Victor Becerra
Michael Hann
Patricio Lau
Fabiana Barnabe
Rob Guido





IVF FLORIDA Reproductive Associates

FIU Herbert Wertheim College of Medicine