Pregnancy in the Patient Over 35 Years of Age

John R. Barton, MD, RDMS
Disclosure of Relevant Financial Relationships

Consultation

• rEVO Biologics
  Data Monitoring Committee
  (Biomarkers and treatment of preeclampsia)
Learning Objectives

• Review heightened perinatal risks associated with increasing maternal age.
• Discuss the importance of optimizing control of chronic illnesses prior to conception in women with increasing maternal age.
• Compare pregnancy outcomes in obese versus non-obese older women.
Disasters Waiting to Happen
Is She Just Too Old For This?
New parents over 50—child-rearing’s final frontier.
By Lisa Miller
Increase in Pregnancy Rates among Women Age 30 and Older

Per 1,000

- 15-19
- 20-24
- 25-29
- 30-34
- 35-39
- 40-44
- 45-49

Year:
- 1970
- 1975
- 1980
- 1985
- 1990
- 1995
- 2000
- 2005
- 2010
Proportion of births by age of mother in USA (left) and UK (right) from 1990 to 2013
Per cent birth rates by women aged 35 and higher, selected countries, 1980–2007.
Why are women waiting?

• Education and Career
  – Enjoy their jobs and don’t want to give them up for motherhood.
• Don’t want child care providers raising their children; wait until they are financially stable.
• Disturbed by the high divorce rate.
• Putting off marriage; don’t want to be a single parent.
Why are women waiting?

• Lack of financial resources to start a family.
• Still live with their parents.
• Reproductive technology has put less stress on the “biological clock”.
• USA does not support young families as other high income nations.
There are both risks and benefits to postponing motherhood.
Increased levels of education have been achieved.
Their children have a higher chance of graduating from high school and attending college.
Community Chest

GO TO JAIL
Go Directly to Jail
DO NOT PASS GO
DO NOT COLLECT $200
Their children spend **less** time in jail (but not less likely to go to jail)
Risks with AMA

- Infertility
- Fetal aneuploidy
- Gestational diabetes, GHTN
- Postpartum incontinence
- Cesarean delivery
- Multiple gestation
- Perinatal mortality
- Maternal mortality
- Advanced paternal age
Fertility and fecundity decrease with age
Why does fertility decline with increasing maternal age?

- Decline in the *number* of eggs
  - Every month there is loss of a group of eggs

- Decline in the *quality* of eggs
  - As the egg ages, errors in the dividing embryo increase
  - These errors may result in aneuploidy
Prevalence of genetically abnormal oocytes in infertile women
## Pregnancy Loss by Maternal Age at Conception

<table>
<thead>
<tr>
<th>Maternal age (years)</th>
<th>Spontaneous abortions (%)</th>
<th>Ectopic pregnancies (%)</th>
<th>Stillbirths rate/1000</th>
</tr>
</thead>
<tbody>
<tr>
<td>12-19</td>
<td>13.3</td>
<td>2.0</td>
<td>5.0</td>
</tr>
<tr>
<td>20-24</td>
<td>11.1</td>
<td>1.5</td>
<td>4.2</td>
</tr>
<tr>
<td>25-29</td>
<td>11.9</td>
<td>1.6</td>
<td>4.0</td>
</tr>
<tr>
<td>30-34</td>
<td>15.0</td>
<td>2.8</td>
<td>4.4</td>
</tr>
<tr>
<td>35-39</td>
<td>24.6</td>
<td>4.0</td>
<td>5.0</td>
</tr>
<tr>
<td>40-44</td>
<td>51.0</td>
<td>5.8</td>
<td>6.7</td>
</tr>
<tr>
<td>&gt;=45</td>
<td>93.4</td>
<td>7.0</td>
<td>8.2</td>
</tr>
</tbody>
</table>

Anderson FWJ, Johnson TRB. Postgraduate Obstetrics and Gynecology 2000; 20:1
<table>
<thead>
<tr>
<th>Maternal Age</th>
<th>DS Risk Birth</th>
<th>All Chrom Abn Birth</th>
<th>DS Risk Mid-trimester</th>
</tr>
</thead>
<tbody>
<tr>
<td>20</td>
<td></td>
<td></td>
<td>1/1231</td>
</tr>
<tr>
<td>30</td>
<td>1/185</td>
<td>1/384</td>
<td>1/685</td>
</tr>
<tr>
<td>33</td>
<td>1/592</td>
<td>1/285</td>
<td>1/452</td>
</tr>
<tr>
<td>34</td>
<td>1/465</td>
<td>1/243</td>
<td>1/352</td>
</tr>
<tr>
<td>35</td>
<td>1/385</td>
<td>1/178</td>
<td>1/274</td>
</tr>
<tr>
<td>36</td>
<td>1/287</td>
<td>1/149</td>
<td>1/213</td>
</tr>
<tr>
<td>37</td>
<td>1/225</td>
<td>1/123</td>
<td>1/166</td>
</tr>
<tr>
<td>38</td>
<td>1/177</td>
<td>1/105</td>
<td>1/129</td>
</tr>
<tr>
<td>39</td>
<td>1/139</td>
<td>1/80</td>
<td>1/100</td>
</tr>
<tr>
<td>40</td>
<td>1/109</td>
<td>1/63</td>
<td>1/80</td>
</tr>
<tr>
<td>41</td>
<td>1/85</td>
<td>1/48</td>
<td>1/61</td>
</tr>
</tbody>
</table>
WHEN MEIOSIS FAILS

Normal Sex cell production

Non-disjunction

Sex Cells

Trisomy 21

Monosomy 21

Blame the spindle fibers

Sex Cells

Zygotes
Trisomy 21 Tidbits

- ~ 70% T21 due to an error in maternal meiosis I
- ~ 20% maternal meiosis II
- ~ 5% occur during spermatogenesis (meiosis II)
- ~ 5% of trisomic 21 error in mitosis

There is no preference for which chromosome 21 is duplicated in the mitotic error
The risks associated with pregnancy in women aged 35 years or older

<table>
<thead>
<tr>
<th>Outcome</th>
<th>18-35 years old</th>
<th>35-40 years old</th>
<th>&gt; 40 years old</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gestational diabetes</td>
<td>1%</td>
<td>2.85%</td>
<td>4.56%</td>
</tr>
<tr>
<td>Placenta previa</td>
<td>0.26%</td>
<td>0.56%</td>
<td>0.97%</td>
</tr>
<tr>
<td>Breech position</td>
<td>2.61%</td>
<td>3.66%</td>
<td>4.57%</td>
</tr>
<tr>
<td>Preterm birth</td>
<td>6%</td>
<td>6.33%</td>
<td>8.17%</td>
</tr>
</tbody>
</table>

18–34 years (n = 336,462), 35–40 years (n = 41,327), >40 years (n = 7331).
Trends in Preeclampsia

Temporal changes in rates of preeclampsia 1980 to 2010 in the U.S. for 120 million hospital discharges.

Causes of trend:
1. Increased obesity
2. Decrease in smoking
3. Older mothers

### Advanced Maternal Age: Neonatal Outcomes in Women with Mild GHTN Remote from Term

<table>
<thead>
<tr>
<th></th>
<th>≥ 35 yrs (n=379)</th>
<th>20-30 yr (n=379)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>GA delivery (wks)</td>
<td>37.2</td>
<td>37.2</td>
<td>0.56</td>
</tr>
<tr>
<td>Birth weight (gms)</td>
<td>2864</td>
<td>2906</td>
<td>0.40</td>
</tr>
<tr>
<td>Nursery stay (days)</td>
<td>6.3</td>
<td>7.1</td>
<td>0.40</td>
</tr>
<tr>
<td>NICU admit (%)</td>
<td>20.3</td>
<td>20.8</td>
<td>0.92</td>
</tr>
<tr>
<td>Stillbirth</td>
<td>5</td>
<td>0</td>
<td>0.06</td>
</tr>
</tbody>
</table>

Barton et al, AJOG 1997;176:1236.
Delayed Childbearing: Effect of Maternal Age at 1st Childbirth on Pregnancy Outcome and Postpartum Incontinence

H Li, P Osterweil, M Mori and JM Guise
Oregon Health Science University

Funded by the National Institute of Child Health & Human Development
R01 HD41139-04
Risk Of Postpartum Incontinence After Vaginal Delivery

Log(Relative Risk)

Fecal Incontinence

AGE (years)

After 33
Risk Of Postpartum Incontinence
After Vaginal Delivery

After 30
Summary

- 1st childbirth at advanced age was associated with prolonged 2nd stage labor, device assistant, laceration, and characteristics such as constipation.

  All risk factors of pelvic dysfunction

- The risk of urinary incontinence is potentially significant after age 30 yrs and fecal incontinence after age 33 yr among women with vaginal delivery.

- Maternal age may be independently associated with urinary incontinence, while its association with fecal incontinence depended upon obstetric risks and women’s characteristics.
In Vitro Fertilization
By the numbers: Twin Birth in US
Multiple deliveries per 1000 births by maternal age.


© The Author 2011. Published by Oxford University Press on behalf of the European Society of Human Reproduction and Embryology.
C/S rate by maternal age, 2009-2011

Source: CDC/NCHS, National Vital Statistics System
Randomized Trial of Labor Induction in Women 35 Years of Age or Older

- Nulliparous women in the UK
- No high-risk pregnancies
- Randomly assigned to
  - Labor induction between 39 w 0 d - 39 w 6 d
  - Expectant management
  (spontaneous onset of labor or development of medical problem that mandated induction)

<table>
<thead>
<tr>
<th>Mode of delivery</th>
<th>Induction Group (N = 304)</th>
<th>Expectant management Group (N = 314)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cesarean section</td>
<td>98 (32%)</td>
<td>103 (33%)</td>
<td>0.92</td>
</tr>
<tr>
<td>Age 35–37 years</td>
<td>44 (26%)</td>
<td>52 (29%)</td>
<td>0.45</td>
</tr>
<tr>
<td>Age 38–39 years</td>
<td>29 (39%)</td>
<td>27 (39%)</td>
<td>0.99</td>
</tr>
<tr>
<td>Age ≥ 40 years</td>
<td>25 (42%)</td>
<td>24 (38%)</td>
<td>0.56</td>
</tr>
</tbody>
</table>

Stillbirth by Maternal Age
Antepartum vs Intrapartum

Rate per 1000

Maternal age (yrs)

20 - 24  | 25 - 29  | 30 - 34  | 35 - 39  | > 40
Stillbirth | Antepartum | Intrapartum
4.4 | 3.6 | 4.4 | 6.3 | 10.5
0.8 | 3.2 | 3.7 | 5.3 | 9.3
0.6 | 3.2 | 0.6 | 1.0 | 1.2

Hazard of fetal death per 1000 ongoing pregnancies

Stillbirth and AMA

- Lethal congenital and chromosomal anomalies
- Medical complications associated with age
  - Multiple gestations
  - HTN
  - DM
- AMA is an independent risk factor
- Unexplained fetal demise is the only type that is statistically more common (late pregnancy)
Older women are doing better; still much worse than younger women
Factors associated with maternal mortality at advanced maternal age

• Smoking during pregnancy
  – adjusted OR 2.06

• Inadequate use of antenatal care
  – aOR 23.62

• Medical co-morbidities
  – aOR 5.92

• Previous pregnancy problems
  – aOR 2.06

Between 2009 and 2012, 105 cases of maternal deaths aged ≥35 years
766 controls aged ≥35 years

McCall et al  BJOG 2016
Disasters Waiting to Happen
Advanced Paternal Age (APA)

66 years old

72 years old
Sperm Are Also Required!
## Paternal Age Effects: Offspring

### Developmental, psychiatric conditions

<table>
<thead>
<tr>
<th>Condition</th>
<th>Relative Risk</th>
</tr>
</thead>
<tbody>
<tr>
<td>Autism</td>
<td>5.7</td>
</tr>
<tr>
<td>Schizophrenia</td>
<td>3 - 4.6</td>
</tr>
<tr>
<td>Autism spectral disorder</td>
<td>1.4 - 3.5</td>
</tr>
<tr>
<td>Neurocognitive impairment</td>
<td>1.1</td>
</tr>
<tr>
<td>Dyslexia</td>
<td>2</td>
</tr>
<tr>
<td>Bipolar disorder</td>
<td>2</td>
</tr>
<tr>
<td>Alzheimer disease</td>
<td>?</td>
</tr>
</tbody>
</table>
### Autism Spectrum Disorder and APA

<table>
<thead>
<tr>
<th>Age of man</th>
<th>Number of chromosome replications in germ cell</th>
<th>Risk for ASD de novo mutations</th>
</tr>
</thead>
<tbody>
<tr>
<td>15 years</td>
<td>35</td>
<td>LOW</td>
</tr>
<tr>
<td>20 years</td>
<td>150</td>
<td></td>
</tr>
<tr>
<td>30 years</td>
<td>380</td>
<td></td>
</tr>
<tr>
<td>40 years</td>
<td>610</td>
<td></td>
</tr>
<tr>
<td>50 years</td>
<td>840</td>
<td>HIGH</td>
</tr>
</tbody>
</table>

As the age of a man increases, the number of divisions that his reproductive or germ cell undergoes increases as well. This rises the risk for ASD by de novo germline mutations.

Crow J.F. Nature Reviews Genetics 2000
<table>
<thead>
<tr>
<th>Single Gene Mutations: Paternal Age Effect Disorders</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Achondroplasias</strong> <em>(FGFR3)</em></td>
</tr>
<tr>
<td><strong>Apert syndrome</strong> <em>(FGFR2)</em></td>
</tr>
<tr>
<td><strong>Crouzon syndrome</strong> <em>(FGFR2)</em></td>
</tr>
<tr>
<td><strong>Hemophilia A</strong></td>
</tr>
<tr>
<td><strong>Marfan syndrome</strong> <em>(FGFR3)</em></td>
</tr>
<tr>
<td><strong>Neurofibromatosis</strong></td>
</tr>
<tr>
<td><strong>Osteogenesis Imperfecta</strong> <em>(FGFR3)</em></td>
</tr>
<tr>
<td><strong>Pfeiffer syndrome</strong> <em>(FGFR2)</em></td>
</tr>
<tr>
<td><strong>Polyposis coli</strong></td>
</tr>
<tr>
<td><strong>Treacher-Collins syndrome</strong></td>
</tr>
<tr>
<td><strong>Wardenburg syndrome</strong></td>
</tr>
<tr>
<td><strong>Aniridia</strong></td>
</tr>
<tr>
<td><strong>Bilateral retinoblastoma</strong></td>
</tr>
<tr>
<td><strong>Fibrodysplasia ossificans</strong></td>
</tr>
<tr>
<td><strong>Lesch Nyhan syndrome</strong></td>
</tr>
<tr>
<td><strong>MEN II</strong> <em>(RET)</em></td>
</tr>
<tr>
<td><strong>Oculodentodigital syndrome</strong></td>
</tr>
<tr>
<td><strong>Polycystic kidney disease</strong></td>
</tr>
<tr>
<td><strong>Progeria</strong></td>
</tr>
<tr>
<td><strong>Thanatophoric dyspl.</strong> <em>(FGFR3)</em></td>
</tr>
<tr>
<td><strong>Tuberous sclerosis</strong></td>
</tr>
</tbody>
</table>
## Risk of the parent dying before the child becomes an adult

### Maternal age at childbirth (years)

<table>
<thead>
<tr>
<th>Maternal age at childbirth (years)</th>
<th>25</th>
<th>30</th>
<th>35</th>
<th>40</th>
<th>45</th>
</tr>
</thead>
<tbody>
<tr>
<td>Risk of mother not surviving until child’s 18(^{th}) birthday (%)</td>
<td>1.0</td>
<td>1.6</td>
<td>2.6</td>
<td>3.8</td>
<td>5.5</td>
</tr>
<tr>
<td>Risk of father not surviving until child’s 18(^{th}) birthday (%)</td>
<td>2.2</td>
<td>3.3</td>
<td>5.4</td>
<td>8.3</td>
<td>12.1</td>
</tr>
</tbody>
</table>

Computations based on mortality tables for France, 2007
"Demographic and medical consequences of the postponement of parenthood". Human Reproduction Update 18 (1): 29–43
What’s an Older Woman to Do?
### Spontaneously Conceived Pregnancy after 40: Influence of Age and Obesity on Outcome

<table>
<thead>
<tr>
<th></th>
<th>Obese</th>
<th>Non-Obese</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>20-29 yrs</td>
<td>≥40 yrs</td>
</tr>
<tr>
<td></td>
<td>n=9224</td>
<td>n=228</td>
</tr>
<tr>
<td>Cesarean</td>
<td>47.0%</td>
<td>69.3%&lt;sup&gt;1&lt;/sup&gt;</td>
</tr>
<tr>
<td>Stillbirth</td>
<td>0.3%</td>
<td>0.9%</td>
</tr>
<tr>
<td>Neonatal death</td>
<td>0.2%</td>
<td>0.4%</td>
</tr>
</tbody>
</table>

<sup>1</sup> <0.05; 20-29 y vs ≥ 40 y within obese or non-obese. Barton et al, *Am J Perinatol* 2014
Spontaneously Conceived Pregnancy after 40: Influence of Age and Obesity on Outcome

Barton et al, Am J Perinatol 2014
“Based on the current state of evidence, modern procedures to cryopreserve oocytes should no longer be considered experimental. The American College of Obstetricians and Gynecologists’ Committee on Gynecologic Practice endorses the joint document and encourages its use by Fellows. There are not yet sufficient data to recommend oocyte cryopreservation for the sole purpose of circumventing reproductive aging in healthy women.”
Preimplantation Genetic Diagnosis (PGD)

- PGD technology involves examination of the chromosomes contained in the polar body taken from an egg or a blastomere from a developing embryo.
- Select embryos free of chromosomal abnormalities and specific genetic disorders for transfer to the uterus.
What’s an Older Woman to Do? Preconception

- Identify risk factors
  - i.e., diabetes, obesity, hypertension
- Optimize maternal health
- Ideal body weight
- Begin folic acid supplementation
- Encourage smoking cessation
- If the patient is ≥45 years old:
  - ECG, glucose screening, Echo if CHTN

Barton, Sibai  OBG Management 2014
What’s an Older Woman to Do?

First trimester

- Ultrasound
  - Dating, assess fetal number and chorionicity
- Baseline metabolic profile and CBC
- Baseline urinalysis
- Continue folic acid supplementation
- Offer first-trimester genetic testing or other genetic screening

Barton, Sibai   OBG Management 2014
What’s an Older Woman to Do?
Second trimester

- If 1st trimester genetic testing is declined, offer second-trimester testing or screening
- Detailed fetal anomaly evaluation by ultrasound
- Fetal echocardiogram if pregnancy
  - By in-vitro fertilization
  - Monochorionic twin gestation
- Screen for gestational diabetes
What’s an Older Woman to Do?

Third trimester

- Increased antenatal testing for routine indications
  - Hypertension, diabetes, lupus
- Ultrasonography for growth and later findings of fetal aneuploidy
- Consider delivery by 40 weeks’ gestation, given the increased risk of stillbirth after a term gestation

Barton, Sibai  OBG Management 2014
Thank You!
References


References


References

• Barton JR, Sibai BM. Optimal obstetric care for women aged 40 and older. OBG Management 2014;26:28,30-34,36-37,e1.


• Vaughn DA, Cleary BJ, Murphy DJ. Delivery outcomes for nulliparous women at the extremes of maternal age—a cohort study. BJOG. 2014;121:261–268.


References


Disasters Waiting to Happen
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