Advanced Maternal Age and Perinatal Outcomes

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I have no disclosures
Learning Objectives

1. Explain the effect of advanced maternal age on perinatal outcomes
2. Discuss specific considerations related to very advanced maternal age
3. Recognize how management may be different in women of advanced maternal age
Definition and Prevalence

- Advanced maternal age (AMA) defined as maternal age 35 or more at delivery
  - Initially identified as cut off point in risk stratification because Down Syndrome risk approximated miscarriage risk from amniocentesis at age 35
- Women giving birth at 45 or older often characterized as very advanced maternal age
Definitions and Prevalence

Definition affected by considerations below:

• Sociologic
• Ethnic
• Cultural considerations

Most likely effects of increasing age on pregnancy outcome occur more as a continuum
Definitions and Prevalance

• Mean age at childbearing (MAC) worldwide declined from 29.1 years in 1950-1955 to 27.5 years in 1990-1995 and remained at level until 2015

• In Europe MAC rose from 26.5 years in 1980-1985 to 29.4 years in 2010-2015

• Mean age at first delivery in industrialized countries increased in last half century from 23 to 25 years in the 1970s to 27-29 years in 2017
Definitions and Prevalance

- **Per CDC report**
  - Reported prevalence of first births among women 35 years old was 7.5% in 2009 and 9.1% in 2014

- **Over last 30 years a rise observed in women having babies at much older ages**
  - In 2010, 0.07% of births were to women 45 and older
  - In 2017, 0.09% of births were to women 45 and older
U.S. birth rate in very AMA women by race/ethnicity

2017 data:

White – 0.07%
Black – 0.1%
Native American – 0.04%
Asian – 0.18%
LatinX – 0.1%
In Los Angeles County, birth rates to younger women are decreasing while those to older women increasing.
Reasons for delayed childbearing in Los Angeles County

- Social: getting married later
- Educational: pursuit of higher education
- Economic: decision to establish career before childbearing; greater access to contraceptives and assisted reproductive technologies; cost associated with raising child

- For a woman in Los Angeles County in 2011, mean age at first birth was 27.1 years, 1.5 years older than U.S. average (25.6 years).

- In 2010, the rate of women having children at 45 and older was 3 fold higher than in 2000
Impact of AMA on fertility

- Fertility gradually declines as women mature starting at age 32 due to decline in oocyte quality and quantity
- Fecundity declines more rapidly at age 37
  - Results in increased demand for ART services
  - Women with pathologic conditions, poor oocyte quality, diminished ovarian reserve or primary ovarian insufficiency can opt for oocyte donation
Impact of AMA on first trimester complications

- ART is risk factor for ectopic pregnancy
- In spontaneous pregnancies combination of risk factors over time (multiple partners, pelvic infections, prolonged smoking, tubal pathology, decreased tubal function and delay of oocyte transportation) lead to higher risk of ectopic
- Higher risk of spontaneous abortion in the setting of chromosomal abnormalities
- Higher incidence of non chromosomal congenital abnormalities
  - Compared to mothers 25-29 years old, women aged 40 and greater have a 2 fold increased risk of congenital abnormalities
Chromosomal risks associated with AMA

- Risk of chromosomal abnormalities increases with maternal age

<table>
<thead>
<tr>
<th>Maternal age at delivery</th>
<th>Risk of trisomy 21</th>
<th>Risk of any chromosomal abnormality</th>
</tr>
</thead>
<tbody>
<tr>
<td>20</td>
<td>1/1667</td>
<td>1/526</td>
</tr>
<tr>
<td>22</td>
<td>1/1429</td>
<td>1/500</td>
</tr>
<tr>
<td>24</td>
<td>1/1250</td>
<td>1/476</td>
</tr>
<tr>
<td>26</td>
<td>1/1176</td>
<td>1/476</td>
</tr>
<tr>
<td>27</td>
<td>1/1111</td>
<td>1/455</td>
</tr>
<tr>
<td>28</td>
<td>1/1053</td>
<td>1/435</td>
</tr>
<tr>
<td>29</td>
<td>1/1000</td>
<td>1/417</td>
</tr>
<tr>
<td>30</td>
<td>1/952</td>
<td>1/385</td>
</tr>
<tr>
<td>31</td>
<td>1/909</td>
<td>1/385</td>
</tr>
<tr>
<td>32</td>
<td>1/769</td>
<td>1/322</td>
</tr>
<tr>
<td>33</td>
<td>1/602</td>
<td>1/286</td>
</tr>
<tr>
<td>34</td>
<td>1/485</td>
<td>1/238</td>
</tr>
<tr>
<td>35</td>
<td>1/378</td>
<td>1/192</td>
</tr>
<tr>
<td>36</td>
<td>1/289</td>
<td>1/156</td>
</tr>
<tr>
<td>37</td>
<td>1/224</td>
<td>1/127</td>
</tr>
<tr>
<td>38</td>
<td>1/173</td>
<td>1/102</td>
</tr>
<tr>
<td>39</td>
<td>1/136</td>
<td>1/83</td>
</tr>
<tr>
<td>40</td>
<td>1/106</td>
<td>1/66</td>
</tr>
<tr>
<td>41</td>
<td>1/82</td>
<td>1/53</td>
</tr>
<tr>
<td>42</td>
<td>1/63</td>
<td>1/42</td>
</tr>
<tr>
<td>43</td>
<td>1/49</td>
<td>1/33</td>
</tr>
<tr>
<td>44</td>
<td>1/38</td>
<td>1/36</td>
</tr>
<tr>
<td>45</td>
<td>1/30</td>
<td>1/21</td>
</tr>
<tr>
<td>46</td>
<td>1/23</td>
<td>1/16</td>
</tr>
<tr>
<td>47</td>
<td>1/18</td>
<td>1/13</td>
</tr>
<tr>
<td>48</td>
<td>1/14</td>
<td>1/10</td>
</tr>
<tr>
<td>49</td>
<td>1/11</td>
<td>1/8</td>
</tr>
</tbody>
</table>

Impact of AMA on late pregnancy complications

• Increased risk of maternal mortality and severe morbidity

• Mortality rates increased from 10.8/10,000 births in women <35 to 38/10,000 birth in women 35 and older

• Increase likely due to presence of comorbidities and coexisting medication conditions
  • Metabolic syndrome
  • Past and current cancer
  • Cardiovascular
  • Renal
  • Autoimmune Diseases
Impact of AMA on late pregnancy complications

- Women >35 are at a 2-4 fold increased risk of hypertension compared to women 30-34 years old which in turn leads to higher risk of preeclampsia

- Preeclampsia incidence is 3-4 % in general population, 5-10% in women 40 and older and 35% in women 50 and older

- Pregestational diabetes and GDM is 3-6 fold higher in women over 40 and 30% in women 50 and older

- Higher risk of placental abruption, placenta previa (10 fold higher risk)
Association of AMA and Labor and Delivery Complications

• Between 2003 and 2012 C/S rate by age climbed:
  • Age 25-34: 20%
  • Age 45-49: 36%
  • 50 and over: 61%

• Higher risk of second stage labor dystocia (even adjusting for GDM and preeclampsia)

• Portion of increase rate is driven by maternal and provider preference
Cesarean Delivery

Figure 7. Forest plot representing the likelihood of delivering through CS in women ≥45 years of age compared with women <45 years of age.

Risks associated with very AMA
Association of AMA and Labor and Delivery Complications

- Relative safety and perceived advantages of low risk Cesarean may be leading to acceptance for non-medical and non-obstetrical indications
  - Lavecchia et al found AMA women with planned Cesarean vs AMA women with planned vaginal delivery had:
    - Higher mortality (2 fold higher risk)
    - Higher peripartum hysterectomy
    - Higher cardiac arrest
    - Higher acute renal failure
    - Higher sepsis
Association between AMA and perinatal mortality and morbidity

- Low birth weight and preterm delivery more prevalent in AMA group even after adjusting for smoking and coexisting morbidities

- Very low birth weight (<1500g) for women 35-40 with singletons 1.9 fold higher compared to women 20-24

- Risk of stillbirth in women 40-44 at 39 weeks was identical to risk of stillbirth in women 25-29 at 42 weeks
Risks associated with very AMA

Intrauterine Fetal Demise

Figure 2. Forest plot representing the likelihood of fetal loss in women ≥45 years of age compared with women <45 years of age.

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>Maternal age ≥45</th>
<th>Maternal age &lt;45</th>
<th>OR M-H, Random, 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Events</td>
<td>Total</td>
<td>Events</td>
<td>Total</td>
</tr>
<tr>
<td><strong>Total (95% CI)</strong></td>
<td><strong>49666</strong></td>
<td><strong>24714561</strong></td>
<td><strong>100.0%</strong></td>
</tr>
<tr>
<td>Total events</td>
<td>2142</td>
<td>176350</td>
<td></td>
</tr>
<tr>
<td>Heterogeneity: Tau² = 0.41; Chi² = 396.00, df = 4 (P &lt; 0.00001); I² = 99%</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Test for overall effect: Z = 3.27 (P = 0.001)</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Risks associated with very AMA

IUGR

Figure 4. Forest plot representing the likelihood of IUGR in women ≥45 years of age compared with women <45 years of age.

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>Maternal age ≥ 45</th>
<th>Maternal age &lt; 45</th>
<th>OR M-H, Random, 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Events</td>
<td>Total</td>
<td>Events</td>
</tr>
<tr>
<td>Mehta et al. 2013</td>
<td>9</td>
<td>64</td>
<td>9</td>
</tr>
<tr>
<td>Phadungkiatwattana et al. 2014</td>
<td>9</td>
<td>82</td>
<td>13</td>
</tr>
<tr>
<td>Shrim et al. 2010</td>
<td>6</td>
<td>63</td>
<td>93</td>
</tr>
<tr>
<td>Yoge et al. 2010</td>
<td>1</td>
<td>177</td>
<td>11</td>
</tr>
<tr>
<td>Total (95% CI)</td>
<td>386</td>
<td></td>
<td>6747</td>
</tr>
</tbody>
</table>

Total events: 25 events in ≥45 group, 126 events in <45 group.

Heterogeneity: Tau² = 0.08; Chi² = 3.85, df = 3 (p = 0.28); I² = 22%
Test for overall effect: Z = 1.50 (p = 0.13)
Risks associated with very AMA

Likelihood of Complications of Pregnancy

Figure 5. Forest plot representing the likelihood of complications of pregnancy (hyperemesis, hypertension disorder in pregnancy, diabetes, placental previa, placental accrete/incrreta in women ≥45 years of age compared with women <45 years of age.
Risks associated with very AMA

Preterm Birth

Figure 6. Forest plot representing the likelihood of preterm birth in women ≥45 years of age compared with women <45 years of age.

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>Maternal age ≥ 45</th>
<th>Maternal age &lt; 45</th>
<th>OR</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.1</td>
<td>Events</td>
<td>Total</td>
<td>Events</td>
</tr>
<tr>
<td>Canterino et al. 2004</td>
<td>711</td>
<td>18335</td>
<td>244512</td>
</tr>
<tr>
<td>Carolan et al. 2013</td>
<td>98</td>
<td>217</td>
<td>9986</td>
</tr>
<tr>
<td>Dulitzki et al. 1998</td>
<td>2</td>
<td>109</td>
<td>3</td>
</tr>
<tr>
<td>Jacquemyn et al. 2014</td>
<td>116</td>
<td>421</td>
<td>5149</td>
</tr>
<tr>
<td>Laskov et al. 2012</td>
<td>67</td>
<td>278</td>
<td>39</td>
</tr>
<tr>
<td>Luke et al. 2007</td>
<td>2604</td>
<td>18335</td>
<td>764996</td>
</tr>
<tr>
<td>Phadungkhiatkattana et al. 2014</td>
<td>35</td>
<td>82</td>
<td>86</td>
</tr>
<tr>
<td>Shrim et al. 2010</td>
<td>10</td>
<td>63</td>
<td>158</td>
</tr>
<tr>
<td>Yoge et al. 2010</td>
<td>59</td>
<td>177</td>
<td>982</td>
</tr>
</tbody>
</table>

Total (95% CI) | 38017 | 16221724 | 100.0% | 1.96 [1.61, 2.39] |

Total events | 3702 | 1025911 |

Heterogeneity: Tau² = 0.06; Chi² = 88.05, df = 8 (P < 0.000001); I² = 91%
Test for overall effect: Z = 6.63 (P < 0.000001)
Los Angeles County Data for perinatal complications

- Very AMA compared to younger women associated with:
  - a 3-6 fold higher incidence of preexisting and gestational diabetes
  - a 5% to 10% rate of preeclampsia – as compared 3% to 4%
  - 16.4% vs 9.3% rate of premature births
  - 16.5% vs 8.6% rate of low birth weight

RollinAlamillo L. et al. 24
Los Angeles County Data for perinatal complications

![Graph showing perinatal complications by age group.](image)

- Early Preterm: Less than 34 weeks
- Late Preterm: 34 weeks to 36 weeks and 6 days
Los Angeles County Data for perinatal complications

Low Weight Births by Mother’s Age
Los Angeles County, 2007 to 2012

- Very Low Birth Weight\(^\ddagger\)
- Low Birth Weight\(^\S\)

\[\text{AGE (YEARS)} \times \text{% OF BIRTHS}\]

\[\begin{array}{c|c|c}
\text{20-24} & 5.5\% & 1.1\% \\
\text{25-29} & 5.4\% & 1.1\% \\
\text{30-34} & 5.8\% & 1.2\% \\
\text{35-39} & 6.7\% & 1.5\% \\
\text{40-44} & 8.6\% & 2.0\% \\
\text{45-49} & 16.5\% & 3.7\% \\
\end{array}\]

\[\ddagger\text{Less than 1,500 grams}, \quad \S\text{1,500 to 2,499 grams}\]
**Risks associated with very AMA**

### Abnormal 5 minute Apgar

Figure 3. Forest plot representing the likelihood of an abnormal 5-minute APGAR score in neonates of women ≥45 years of age compared with women <45 years of age.

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>Maternal age ≥ 45</th>
<th>Maternal age &lt; 45</th>
<th>Weight</th>
<th>OR</th>
<th>M-H, Random, 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Grotegut et al. 2014</td>
<td>590</td>
<td>23807</td>
<td>22470</td>
<td>1836403</td>
<td>33.2%</td>
</tr>
<tr>
<td>Kort et al. 2011</td>
<td>2</td>
<td>74</td>
<td>1</td>
<td>23</td>
<td>5.1%</td>
</tr>
<tr>
<td>Laskov et al. 2012</td>
<td>8</td>
<td>278</td>
<td>8</td>
<td>304</td>
<td>17.5%</td>
</tr>
<tr>
<td>Phadungkhatwattana et al. 2014</td>
<td>16</td>
<td>82</td>
<td>8</td>
<td>328</td>
<td>19.3%</td>
</tr>
<tr>
<td>Yogevo et al. 2010</td>
<td>12</td>
<td>177</td>
<td>141</td>
<td>5310</td>
<td>24.9%</td>
</tr>
<tr>
<td><strong>Total (95% CI)</strong></td>
<td><strong>24418</strong></td>
<td><strong>1842368</strong></td>
<td><strong>100.0%</strong></td>
<td></td>
<td><strong>2.49 [1.37, 4.54]</strong></td>
</tr>
<tr>
<td><strong>Total events</strong></td>
<td><strong>628</strong></td>
<td><strong>22628</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Heterogeneity: $\tau^2 = 0.28; \text{Chi}^2 = 14.82, df = 4 (P = 0.005); I^2 = 73\%$

Test for overall effect: $Z = 2.98 (P = 0.003)$
Association between AMA and postpartum complications

• Correlation between AMA and postpartum complications less known

• Strong correlation shown between AMA and:
  • Postpartum hemorrhage
  • Fever
  • Need for blood transfusion
  • Prolonged hospitalization
Risks associated with very AMA

Periconception Hemorrhage

Figure 8. Forest plot representing the likelihood of periconception hemorrhage (transfusion, hysterectomy, rate of ICU admission) in women ≥45 years of age compared with women <45 years of age.
AMA and multiples

- AMA linked to higher use of ART which in turn leads to higher incidence of multiples

- Data mixed on outcomes with AMA and non AMA women with multiples
  - Some found similar outcomes in both groups
  - Others found AMA pregnancies with twins to have higher incidence of GDM, hypertensive disorders, Cesarean, postpartum hemorrhage, preterm delivery, low birth weight and NICU admission
  - Women 45 and older at a 3 fold higher risk of hypertensive disorders and preterm delivery, neonatal hypoglycemia and NICU admission

Delbaere et al, Zhu et al, McLennan et al, Lee et al, Avnon et al
Maternal age or oocyte age?

- Compared to spontaneous pregnancies and other ART pregnancies, Oocyte Donation (OD) pregnancies carry a higher risk of hypertensive disorders, preterm birth and low gestational birth.

- Very AMA women with OD had a 12 fold increase of hypertensive complications compared to very AMA women with spontaneous pregnancies.
Advanced Paternal Age

- Advanced paternal age has also climbed in the US
  - Percentage of all births to fathers >40 doubled since the 1970s

- After adjustment for advanced maternal age, paternal age >45 associated with increased risk:
  - Preterm birth
  - Stillbirth
  - Musculoskeletal syndromes
  - Cleft palate
  - Acute lymphoblastic leukemia
  - Retinoblastoma
  - Neurodevelopmental disorder such as autism spectrum and schizophrenia
  - Higher risk of maternal outcomes such as GDM and preeclampsia

Khandwala et al 32
Psychological Impact

- Women 35 and older have higher rate of depressive symptoms compared to younger women

But...

- Women 35 and older
  - more easily adapted their lifestyle to parenthood
  - showed better parenting skills
  - had more social support
  - children did better at school

Bornstein et al, Lee et al and Zybert et al
Long Term Implications

• Age-adjusted mortality rate starting at age 55 were highest for childless women (9.2 per 1000)

• Parity has more influence on longevity than late age at delivery

• Impact of AMA at first delivery not clear

• Delayed first pregnancy risk factor for breast cancer (compared to nulliparous women - 20% lower if first child at age 20, 10% lower if first child at age 25 and 5% higher if first child at age 35)

• Studies from Taiwan found parity and younger age at first delivery may confer protective effect on risk of death from brain cancer, colon cancer and chronic renal failure

Jaffe et al, Collaborative Group on Hormonal Factors in Breast Cancer, Chiu et al, Kuo et al
Management

- Evaluation for chromosomal abnormalities
- Evaluation for underlying heart disease (EKG, BP)
- Evaluation for underlying diabetes
- Breast cancer screening (mammogram)
- Colon Cancer screening (colonoscopy if age appropriate)
- Baby aspirin for preeclampsia prevention
- Detailed Fetal evaluation for anomalies
- Surveillance of fetal growth
- Antenatal testing in the third trimester
- Delivery by 39 weeks
Take Away Points

- Advanced maternal age associated with significantly higher risk of perinatal complications
  - Decrease in fertility
  - Increased need for ART
  - Increased risk of chromosomal and genetic disorders
  - Higher incidence of first trimester loss
  - Higher risk of late pregnancy complications
    - Hypertensive disease
    - GDM
    - Preterm Birth
    - Fetal Growth Restriction
    - SGA
    - Stillbirth

Hypertensive disease
- GDM
- Preterm Birth
- Fetal Growth Restriction
- SGA
- Stillbirth
Take Away Points

• Some ethical issues:
  • Ovum donation and attempt to restore pregnancy potential after menopause (how old is too old?)
  • Interventions to decrease complications
    ◦ Preconception counseling and screening
    ◦ Early pregnancy primary prevention treatment
    ◦ Close pregnancy monitoring
    ◦ Early induction of labor when indicated
Questions?
References


