ADVANCED MATERNAL AGE AND PREGNANCY OUTCOME

Prof. dr Snezana Crnogorac
Obs & Gyn Clinic Podgorica
Medical Faculty University of Montenegro
Zagreb 2015.
HOW LATE IS TOO LATE?
ADVANCED MATERNAL AGE?

- Over 35 years
- Over 40 years
- Over 45 years (very advanced)
Is Infertility Affected by Age?
YES!! Pregnancy rates sharply decline after age 35
Average age of mother at first birth - USA
Figure 1. The rates (%) of primiparous and multiparous women aged 35 years or older giving birth in Finland 1987–2013. (THL 2014, information of the rates of primiparous and multiparous women in Finland.)
Number of deliveries - Montenegro

Generally drop
Montenegro- deliveries by age
Montenegro - deliveries by age

- Mean maternal age at the birth of the first child increased
  - 1980: 24.3
  - 2009: 26.3
What’s change?

Not just a number

• Structure of the mother is changed
• Age and parity not correlate during reproductive life

• Before - women after 35 had many deliveries

• Now - for majority of them is a first pregnancy with ART
• Number of twins
Why are number of births after 35 increasing?

A) increased number of women aged 35-45
B) later marriages, second marriages
C) better contraceptive options available
D) more opportunities to further education and career
E) ART
Table 1. The results of the literature search of AMA and pregnancy outcomes from three electronic databases between the years 2004–2014

<table>
<thead>
<tr>
<th>Electronic database</th>
<th>Keywords</th>
<th>Number of references</th>
</tr>
</thead>
<tbody>
<tr>
<td>PubMed</td>
<td>&quot;advanced maternal age&quot; AND &quot;pregnancy&quot;</td>
<td>566</td>
</tr>
<tr>
<td>PubMed</td>
<td>&quot;older maternal age&quot; AND &quot;pregnancy&quot;</td>
<td>100</td>
</tr>
<tr>
<td>PubMed</td>
<td>&quot;advanced maternal age&quot; and &quot;pregnancy outcomes&quot;</td>
<td>41</td>
</tr>
<tr>
<td>Cinahl</td>
<td>&quot;advanced maternal age&quot; AND &quot;pregnancy&quot;</td>
<td>13</td>
</tr>
<tr>
<td>Cinahl</td>
<td>&quot;older maternal age&quot; AND &quot;pregnancy&quot;</td>
<td>0</td>
</tr>
<tr>
<td>Cinahl</td>
<td>&quot;advanced maternal age&quot; AND &quot;pregnancy outcomes&quot;</td>
<td>0</td>
</tr>
<tr>
<td>PsycInfo</td>
<td>&quot;advanced maternal age&quot; AND &quot;pregnancy&quot;</td>
<td>15</td>
</tr>
<tr>
<td>PsycInfo</td>
<td>&quot;older maternal age&quot; AND &quot;pregnancy&quot;</td>
<td>9</td>
</tr>
<tr>
<td>PsycInfo</td>
<td>&quot;advanced maternal age&quot; AND &quot;pregnancy outcomes&quot;</td>
<td>0</td>
</tr>
</tbody>
</table>

Total number of included studies in literature review: 23
Advanced maternal age- risks

• Do mothers of advancing age (≥ 35) have increased risks associated with pregnancy?
• What risks do they have?
• How to minimize these risks?
GENERAL RISKS COMPLICATING PREGNANCIES

• Smoking
• Increased body weight and obesity
• Diabetes and gestational diabetes
• Chronic hypertension and preeclampsia
Early Pregnancy Issues

- Risk is higher for some problems:
  - spontaneous abortions
  - ectopic pregnancies
  - chromosomal abnormalities
  - congenital malformations
Risk of Pregnancy Loss

- <30 yrs: ~12%
- 30-34 yrs: ~15%
- 35-39 yrs: ~25%
- 40-44 yrs: ~51%
- >45 yrs: ~93%
Rate of spontaneous abortion
Risk of Spontaneous Abortion with Advancing Age

- Risk increases with age.
- Fertility rate decreases with age.
- Spontaneous abortion rate increases with age.
Miscarriages

- Older women have an increased number of abortions usually due to **decline in oocyte quality**.
- Also, change in **uterine/hormonal function**
Miscarriage after Cardiac Activity on Ultrasound

- The risk of eventual miscarriage in women of advancing age is significant despite the presence of cardiac activity on US:

study of over 2000 IVF pregnancies lost after seeing cardiac activity:

<table>
<thead>
<tr>
<th>Age Range</th>
<th>Risk (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;30 yrs old</td>
<td>~ 5%</td>
</tr>
<tr>
<td>31-34 yrs</td>
<td>~ 8%</td>
</tr>
<tr>
<td>35-39 yrs</td>
<td>~ 13%</td>
</tr>
<tr>
<td>&gt;40 yrs</td>
<td>~ 22%</td>
</tr>
</tbody>
</table>
Ectopic Pregnancy

- Major source of maternal mortality and morbidity
- Studies have shown that >35 years old associated with a 4-8 fold increase
- Higher, why? - multiple partners
  - pelvic infections
  - tubal pathology
## Risk of Down’s Syndrome and Chromosomal Abnormalities

<table>
<thead>
<tr>
<th>Maternal Age at Delivery (yr)</th>
<th>Risk of Down’s Syndrome</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>25</td>
<td>1/1200</td>
<td>1/476</td>
</tr>
<tr>
<td>30</td>
<td>1/952</td>
<td>1/385</td>
</tr>
<tr>
<td>35</td>
<td>1/378</td>
<td>1/192</td>
</tr>
<tr>
<td>40</td>
<td>1/106</td>
<td>1/66</td>
</tr>
<tr>
<td>45</td>
<td>1/30</td>
<td>1/21</td>
</tr>
</tbody>
</table>

(Hook et al)
Chromosomal Abnormalities

- Biological basis--- oocytes reach metaphase I during fetal period and remain on metaphase plate until oocyte is stimulated to divide (prior to ovulation).

- Age related errors appear to increase the risk of nondisjunction leading to unequal chromosome products.

- A steady increase in the risk of aneuploidy as a women age.
Anomalies

Increased rates of congenital abnormalities (cardiac, spina bifida, cleft palate, syndactyly, limb defects and male genital malformations) i.e. baseline risk of congenital abnormalities is 3.5% ≤ 25 year old mother increases to 4.5% in age 35 ≥ and 6% in 40 ≥ (Hollier et al 2000)

**** advanced maternal age associated with all cardiac defects ****
Late Pregnancy Issues

- Some obstetrical issues in older women are related to maternal age.

- Others are related to higher parity and co-existing medical conditions. *(hypertension, diabetes, placental issues)*
Advanced maternal age and adverse perinatal outcome. Jacobsson B1, Ladfors L, Milsom I. National prospective, population-based, cohort study in women aged 40-44 years and 45 years or older control group of women aged 20-29 years who delivered during the period 1987-2001. During the 15-year period, there were 1,566,313 deliveries (876,361 women were 20–29 years of age, 31,662 were 40 – 44 years, and 1,205 were > 45 years. The Swedish Medical Birth Register
Perinatal mortality, intrauterine fetal death, and neonatal death increased with age. There was also an increase in intercurrent illnesses and pregnancy complications with increasing age, but this did not entirely explain the observed increase in perinatal mortality.
HYPERTENSION

Older women have a two fold higher risk of being diagnosed with HTN.

Preeclampsia in general population is 3 to 4% in general population

5 to 10% in women >40
DIABETES

- Prevalence increases with maternal age
- Rates of pre-existing DM and gestational DM increase 3-6 fold in women >40.

DM II

Incidence of gestational DM
- 3% in the general OB population
- ~7-12% in women over age 40
- ~20% in women over age 50
Placental Problems

- Abruptio placenta
- Placenta previa

**nulliparous women >40 have a tenfold increased risk of placenta previa compared to women 20-29 yrs old.**
Clinical Study

Swedish study.... Nulliparous women

173,715 women compared the birth outcome of women 20-24 yrs to 35-40 yrs

Older women had higher risk of LBW and preterm delivery

Rates were almost doubled in the older women by age 45.....
Preterm delivery against maternal age

Maternal age (years)
- Broken line: first pregnancy
- Solid line: second pregnancy

Reference:
Mode of Delivery
(Joseph et al 2002)

• A nulliparous 40 year old or older had less than a 7% chance of a normal vaginal delivery. 50% chance of C-section and 43% chance of operative vaginal delivery.

• 35-39 nulliparous 37.7% chance of C-section and 36.9% chance of operative vaginal delivery

• One in 2 births to women aged 40-54 were delivered by cesarean compared with less than 1 in 4 births to women under age 20.
Caesarean delivery rates by age of mother

Figure 2. Cesarean delivery rates, by age of mother: United States, 1996, 2000, and 2007

MATERNAL MORTALITY
(Jacobsson et al 2009)

- Increased rates of maternal mortality significantly increased in women ≥ 40 and in women ≥ 45 an OR 121 has been reported compared to women aged 20-29 (Jacobsson et al 2009). Thankfully this is still a rare occurrence overall.
- 20-29 1.4/100,000 deliveries
- 40-44 22.1/100,000 deliveries
- > 45 166.00/100,000 deliveries

Jacobsson et al
Maternal Risks

• Increased rates of multiples, hypertension, diabetes, placental abruption, placenta previa, preterm birth, operative vaginal delivery, c-sections, post partum hemorrhage and decreases VBAC (vaginal birth after c-section) rates.

• Increased medical and surgical complications***
THROMBOEMBOLISM EPIDEMIOLOGY

• 1 in 100,000 women of childbearing age

• 1/1000 pregnancies in women under the age of 35

• 4/1000 pregnancies in women over the age of 35
THROMBOEMBOLISM
PREGNANCY RELATED RISK FACTORS
– Venous stasis
– Advanced maternal age
– **Multiparity**
– Gestation < 36 weeks
– Instrument-assisted or caesarean delivery
– Haemorrhage
– **Pre-eclampsia**
– Prolonged labour
Pregnancy-Related Mortality Ratios by Age and Race, US, 1991-97
Perinatal Risks

• Increased rates of LBW in singletons (Prysak at all 1995)
• Increased preterm deliveries, increased SGA infants, both <10% and <3%.(Joseph et al 2002).
• Maternal age of nulliparas is not associated with different birth weight characteristic of their twins (Blickstein et al 2000).
Perinatal Mortality

• Perinatal mortality defined as stillbirth or death within 6 days of birth.
  • 1.4% in 45+ older
  • 1.0% 40-44
  • 0.5% in 20-29 (Jacobsson et al 2009)
• Similar to Canadian study (Joseph et al 2002)
Maternal age and risk of stillbirth: a systematic review
Ling Huang MD MSc, Reg Sauve MD MPH, Nicholas Birkett MD MSc, De
The biological mechanism of the increase in stillbirth risk with advanced maternal age is uncertain.

A direct effect of maternal aging may exist. This would probably be related to low uteroplacental perfusion caused by poor uterine vasculature in older women.

Older women have a higher risk of experiencing pregnancy-induced hypertension or gestational diabetes.

Between 50% and 70% of mothers of still-born infants had medical or pregnancy complications during their pregnancies.
Figure 3. Rates (%) of the higher outcomes in women aged ≥35 years (N=2,387) compared with women <35 years (N=15,437) with preeclampsia.

Publications of the University of Eastern Finland
Dissertations in Health Sciences
270
Longer term risks

- Trisomy in grandchildren (Aageson et al 1984)
- Neurological Disorders ?Autism (King et al 2009)
- Diabetes?
- Male infertility (St. John et al 1997)
Maternal Age and Autism in California: 1990-1999

<table>
<thead>
<tr>
<th>Maternal Age</th>
<th>Autism Cases</th>
<th>Total Births</th>
<th>Cases/Total</th>
<th>Rate Per 1,000</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;25</td>
<td>2,689</td>
<td>1716660</td>
<td>0.00156641</td>
<td>1.57</td>
</tr>
<tr>
<td>25-29</td>
<td>3,304</td>
<td>1409538</td>
<td>0.00234403</td>
<td>2.34</td>
</tr>
<tr>
<td>30-34</td>
<td>3,576</td>
<td>1165466</td>
<td>0.0030683</td>
<td>3.07</td>
</tr>
<tr>
<td>35-39</td>
<td>2,089</td>
<td>543191</td>
<td>0.00384579</td>
<td>3.85</td>
</tr>
<tr>
<td>40 and up</td>
<td>501</td>
<td>113080</td>
<td>0.00443049</td>
<td>4.43</td>
</tr>
</tbody>
</table>
ART

- ART cannot compensate for all of the natural decline in fertility with advancing age.

- Disadvantages - multiple birth rate elevated
  - 2003 data - 22% of births in women age 45-54 were multiples vs. 2% in 1990
Conclusions

It is certainly possible for these women to conceive, have healthy pregnancies, and to bear healthy babies. Advancing age is not a reason to abstain from becoming pregnant, but it does carry increased risks that should be discussed and watched for by the practitioner and the patient.