FACULDADE DE MEDICINA DA UNIVERSIDADE DE COIMBRA

MESTRADO INTEGRADO EM MEDICINA – TRABALHO FINAL

ROSA FIGUEIRA DA CÂMARA LOMELINO PINHEIRO

rosafigueirapinheiro@gmail.com

Advanced Maternal Age: Adverse Outcomes of Pregnancy

ARTIGO CIENTÍFICO

ÁREA CIENTÍFICA DE FISIOPATOLOGIA

Este trabalho foi redigido de acordo com as normas da revista

Acta Obstetricia et Gynecologica Scandinavica (AOGS)

Trabalho realizado sob a orientação de:

ANA LUÍSA FIALHO AMARAL AREIA

ANABELA MOTA PINTO

Janeiro de 2017

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Resumo / Abstract

Introdução: Não há consenso na literatura sobre os riscos da gravidez em mulheres com idade materna avançada (IMA). O objetivo desta meta-análise consistiu em determinar se as mulheres com IMA (≥35) tinham piores desfechos obstétricos e perinatais, comparativamente com as mulheres não-IMA (20-34 anos), em gestações de feto único e por conceção natural.

Materiais e métodos: A pesquisa bibliográfica foi feita na MEDLINE, PubMed, IndexRMP e na *Cochrane Database of Systematic Reviews*. Foram incluídos dez estudos segundo os seguintes critérios: população-estudo >1000 mulheres, nulíparas e/ou multíparas, com gestações de feto único sem recurso a tecnologias de reprodução medicamente assistida. Duas meta-análises foram feitas com o programa RevMan5: uma comparando os desfechos da gravidez do grupo 20-34 anos com o grupo 35-40 anos e outra comparando os grupos de idades 35-40 e >40 anos.

Resultados: As mulheres com 35-40 anos tinham mais probabilidade de ser casadas, não-fumadoras e terem >12 anos de escolaridade, comparativamente ao grupo 20-34 anos OR 1.46 (95%IC; 1.41–1.51), OR 0.75 (0.73–0.77), OR 1.39 (1.36–1.42) e >40 anos OR 0.72 (0.69–0.76), OR 1.13 (1.08–1.18), OR 1.39 (1.36–1.42), respetivamente. Mulheres com IMA (35-40 e >40 anos) tinham maior probabilidade de ter excesso de peso OR 1.18 (1.16–1.20), OR 1.09 (1.06–1.12) e comorbilidades como diabetes gestacional OR 1.87 (1.80–1.95), OR 1.38 (1.31–1.46) e hipertensão gestacional OR 1.07 (1.03–1.11), OR 1.30 (1.23–1.37). Tinham também maior frequência de partos induzidos OR 1.12 (1.11–1.13), OR 1.17 (1.14–1.20) e de cesarianas eletivas OR 2.01 (1.98–2.05), OR 1.38 (1.34–1.42). As mulheres mais velhas tinham mais partos pré-termo OR 1.23 (1.21–1.25), OR 1.17 (1.14–1.21) e recém-nascidos com baixo peso OR 1.10 (1.05–1.15), OR 1.35 (1.25–1.47). Os bebés das mães com IMA eram mais vezes admitidos na Unidade de Cuidados Intensivos Neonatais OR 1.13 (1.10–1.17), OR 1.20 (1.13–1.27) e tinham piores índices de Apgar OR 1.31 (1.27–1.35), OR 1.16

(1.08–1.24). De igual forma, as mulheres com IMA tinham maiores taxas de mortalidade perinatal OR 1.27 (1.20–1.33), OR 1.33 (1.21–1.46) e morte *in utero* OR 1.60 (1.53–1.68), OR 1.33 (1.21–1.46).

Conclusões: Mulheres com IMA têm um maior risco de desfechos obstétricos e perinatais adversos. Em ambas as comparações os piores desfechos foram mais prevalentes no grupo de mulheres com maior idade, sugerindo maior expressão com o avançar da idade.

Palavras-chave: Idade materna avançada, Idade materna, Desfechos da gravidez, Desfechos perinatais, Gravidez tardia.

Introduction: The risks of older motherhood are not consensual amongst studies. The aim of this meta-analysis was to determine if advanced maternal age (AMA) (≥35 years old) women had worse obstetrical and perinatal outcomes, comparatively to non-AMA women (20-34 years old), in singleton, naturally-conceived pregnancies.

Material and methods: We searched MEDLINE, PubMed, IndexRMP and the Cochrane Database of Systematic Reviews. Ten studies were included according to the following criteria: population of >1000 nulliparous and/or multiparous women, with singleton gestations, who did not undergo some type of infertility treatment. Using RevMan5, two meta-analysis were performed: one comparing outcomes of 20-34-year-old with 35-40-year-old women and another comparing the 35-40 with >40 age groups.

Results: Women aged 35-40 years old (YO) were more likely to be married, to be non-smokers and to have >12 years of education, compared to 20-34 YO OR 1.46 (95%CI; 1.41–1.51), OR 0.75 (0.73–0.77), OR 1.39 (1.36–1.42) and >40 YO OR 0.72 (0.69–0.76), OR 1.13 (1.08–1.18), OR 1.39 (1.36–1.42), respectively. AMA women (35-40 and >40 YO) had the highest odds of being overweight OR 1.18 (1.16–1.20), OR 1.09 (1.06–1.12) and having gestational diabetes OR 1.87 (1.80–1.95), OR 1.38 (1.31–1.46) and gestational hypertension

OR 1.07 (1.03–1.11), OR 1.30 (1.23–1.37). They were also more likely to have induced labour OR 1.12 (1.11–1.13), OR 1.17 (1.14–1.20) and elective cesarean deliveries OR 2.01 (1.98–2.05), OR 1.38 (1.34–1.42). Also, they had more preterm deliveries OR 1.23 (1.21–1.25), OR 1.17 (1.14–1.21) and low birthweight babies OR 1.10 (1.05–1.15), OR 1.35 (1.25–1.47). Babies of AMA mothers had higher rates of Neonatal Intensive Care Unit (NICU) admission OR 1.13 (1.10–1.17), OR 1.20 (1.13–1.27) and worse Apgar scores OR 1.31 (1.27–1.35), OR 1.16 (1.08–1.24). AMA women had higher rates of perinatal mortality OR 1.27 (1.20–1.33), OR 1.33 (1.21–1.46) and stillbirth OR 1.60 (1.53–1.68), OR 1.33 (1.21–1.46).

Conclusions: AMA women are at higher risk of adverse obstetrical and perinatal outcomes. In both comparisons worse outcomes were more prevalent in the older group, suggesting more expression with increasing age.

Keywords: Advanced maternal age, Maternal age, Pregnancy outcome, Perinatal outcome, Delayed childbearing.

Abbreviations

AMA, Advanced Maternal Age; ART, Assisted Reproductive Technology; BMI, Body mass index; BW, Birthweight; CI, Confidence interval; CS, Cesarean section; LBW, Low birthweight; NICU, Neonatal Intensive Care Unit; OR, Odds ratio; SGA, Small for gestational age; YO, Years old.

Key message

- Women at advanced maternal age (≥35 years old) have more maternal morbidities and worse perinatal outcomes;
- Women in the older groups consistently have poorer outcomes, meaning that the risks of adverse pregnancy outcomes become more prevalent as age increases.

Introduction

Women are postponing childbearing to theirs late 35s, 40s and beyond, almost all around the world.(1-7)

The common use of contraception and birth control methods allows women to prevent unwanted pregnancies. Moreover, advances in reproductive medicine and infertility treatments make it possible for those women to postpone first pregnancy beyond their own biological and fertile age. It is consensual that the desire to build successful careers and have equal opportunities in the job market, attaining financial stability, are major concerns to most women nowadays.(4, 8) Furthermore, other reasons for delaying first pregnancy are strongly related to lifestyle factors: not being mature enough, not having met a suitable partner.(1, 9)

In less resourced countries, childbearing is commoner amongst multiparous older women due to ineffective family planning methods and favourable cultural disposition towards large family size.(10, 11) In developed countries, the reasons for continuing to have children after a certain age could also be the desire to have a large family and wanting to have children with a second husband.(12)

For most authors, the definition of advanced maternal age (AMA) is 35 years old and above.(13-16) However, often in medical literature the AMA group is considered to be pregnancy over 40 years old.(11, 17, 18)

Most studies conclude that pregnancy at advanced age is seldom without risks. However, those conclusions based on individual obstetrical or perinatal adverse outcomes lack consensus. Some authors even describe specific events that don’t differ between AMA and non-AMA like preterm birth, low birthweight, small for gestational age and perinatal mortality.(5, 13-15, 17, 19)

When hypothesizing the reasons why AMA women have worse outcomes in their pregnancies, there are multiple theories. Some claim age alone is not a risk factor.(13, 15)

According to *Aldrighi et al.*(9) adequate follow-up during the prenatal period and suitable care during childbirth make maternal and perinatal prognoses similar to those of younger pregnant women. Furthermore, the AMA group being mainly composed of well-educated and informed women who have probably waited longer for a desired pregnancy, despite their biologic ageing, may be more prepared and more cautious towards their condition and thus amending for some of the negative factors.(20-23). Opposing this, *Kenny et al.* (24) compared the results after adjusting for socioeconomic status, parity, BMI and maternal smoking and worse outcomes remained evident for the AMA group.

Older childbearing is associated with an increased risk of comorbidities such as obesity, hypertension and diabetes mellitus. *Li et al.*(25) studied a group of low-risk pregnant women and still found more negative outcomes in women aged ≥35 years old comparatively to younger women. This led us to believe pre-existing disease does not fully explain why older women have worse pregnancy outcomes, either.(4, 8, 18)

The purpose of this study was to perform a meta-analysis on the obstetrical and perinatal outcomes of singleton gestations at AMA (35-40 and >40 years old), compared with non-AMA (20-34 years old).

Our study aimed to comprise nulliparous and multiparous women from diverse countries, with different educational and social status with the purpose of attaining a large, yet comparable, sample.

With advances in obstetric care and pregnancy surveillance, we questioned what outcomes have become expectable and manageable or if, despite medical progress, pregnancy after 35 is undeniably an obstetric risk.

Also, we propose some theories that try to explain why the conclusions may vary within studies.

Material and methods

Literature search

The research was performed using MEDLINE through PubMed interface, PubMed, IndexRMP and the Cochrane Database of Systematic Reviews, between 10th February 2015 and 3rd October 2016. We limited our research to available published articles between January 2006 and October 2016 in English and Portuguese languages. Bibliographies and references of relevant retrieved studies and recent reviews were hand-searched for additional publications.

Search terms were "advanced maternal age", "advanced maternal age" AND "pregnancy outcomes", AND "perinatal outcomes", "Pregnancy over 35 years old", "Pregnancy over 40 years old", "Delayed childbearing".

We chose to focus on pregnancy and perinatal outcomes, rather than labour patterns, birth defects or offspring outcomes.

PICO question: Do pregnancies in older women (age ≥35 years) have more maternal morbidities or worse perinatal outcomes?

Study selection

The inclusion criteria defined beforehand were: studies with a study population over 1000 women concerning cohorts, cross-sectional studies, systematic reviews, meta-analysis, surveys and questionnaires; from any country; singleton gestations.

Advanced maternal age (study group) was defined as women over 35 years old but studies considering the advanced maternal age (AMA) group to be women over 40 years old were also admitted.

We excluded articles that admitted women who underwent any type of assisted reproductive technology (infertility treatment, in vitro fertilization or oocyte donation) and articles focusing solely on congenital abnormalities. Moreover, for our meta-analysis, group

studies with large age intervals between them (20-30, >40) were also dismissed. The reason to do so is that age and its effects act like a continuum rather than a threshold.(25-27)

Data acquisition and extraction

First, two of the authors defined specific items to determine the inclusion or exclusion of the articles in the meta-analysis. Any discrepancies were resolved through discussion.

To perform this meta-analysis, data were extracted from recent population (>2006) and hospital-based cohorts and cross-sectional studies with a sample of more than 1000 women, nulliparous and both nulliparous and multiparous, from low-income and high-income countries.

For data analysis, studies were required to have their results in raw numbers or percentages. When such didn't happen, we looked through the author's manuscript to see if it provided the original tables. The percentages were converted to absolute numbers using the excel formula [=*ROUND*(((*B1*B2*)/100);0)].

Ten studies met all the criteria defined above and these were carefully analysed by two of the authors to determine whether they were appropriate for a combined analysis. We attentively studied each article regarding: inclusion and exclusion study-population criteria, data acquisition method, assessment of socioeconomic characteristics and definition of variables.

Finally, after completing the review of the articles, data were extracted by one of the authors.

This meta-analysis was performed in compliance with the PRISMA recommendations.(28)

Data analysis and presentation

The numbers were assessed using RevMan5 which automatically compared and analysed the information. Two analyses were performed: the first one comparing the 20-34 and 35-40 age groups and the second comparing 35-40 and >40.

Variables definition

Concerning maternal sociodemographic characteristics, marital status was defined as either married or cohabiting or not a single parent. Smoking refers to tobacco use in early pregnancy or during pregnancy. Education was divided in ≤12 years or "skilled" and below or "highschool or less" and >12 years or "holding a college degree". Maternal or pre-pregnancy body mass index was categorized as low (<18.5 kg/m^2), normal (18.5–24.9 kg/m^2) and overweight or obese (≥25kg/m^2). Gestational hypertension included preeclampsia. Labour was divided in medically induced and spontaneous. In mode of delivery, vaginal birth included normal/unassisted and operative vaginal delivery. Preterm birth was defined as before 37 weeks of gestation. Birthweight was categorized as follows: very low birthweight (<1500g), low birthweight (1500–2500g) and macrosomia (>4000g). Small for gestational age was defined as birthweight below the 10^{th} percentile of the birthweight-for-gestational ages sex-specific curve. Other neonatal outcomes were Apgar score <7 at 5 minutes and Neonatal Intensive Care Unit admission. Maternal near miss was a woman who nearly died but survived a complication that occurred during pregnancy, childbirth, or within 42 days of termination of pregnancy and maternal death was the death of a woman while pregnant or within 42 days of termination of pregnancy, according to the World Health Organization (WHO).(29) Perinatal mortality was defined as stillbirth and neonatal death (death before 28 completed days after birth) and stillbirth was intrauterine death of a child after 22 weeks of gestation or weighing ≥500g.

The quality of this study was assessed using the CONSORT checklist.(30) Risk of bias was assessed for each study upon verification of methodology and inclusion criteria.

Search examples

1. Advanced[All Fields] AND (“maternal age”[MeSH Terms] OR (“maternal”[All Fields] AND “age”[All Fields]) OR “maternal age”[All Fields])

2. “Pregnancy Outcome”[MeSH Terms]

3. “Advanced Maternal Age” AND (“Pregnancy Outcome”[MeSH Terms]) OR (AND perinatal[All Fields] AND outcomes[All Fields])

4. “Pregnancy”[All Fields] AND (“outcome”[All Fields])

5. “Pregnancy outcome”[All Fields] AND (“maternal age”[MeSH Terms])

6. “Maternal”[All Fields] AND “age”[All Fields]

7. “Maternal Age”[All Fields]) AND 40[All Fields] AND older[All Fields]

8. “Pregnancy”[MeSH Terms] OR “pregnancy”[All Fields]) AND over[All Fields] AND 35[All Fields] AND years[All Fields] AND old[All Fields]

9. (“Pregnancy”[MeSH Terms] OR “pregnancy”[All Fields]) AND over[All Fields] AND 40[All Fields] AND years[All Fields] AND old[All Fields]

10. Advanced[All Fields] AND (“maternal age”[MeSH Terms] OR (“maternal”[All Fields] AND “age”[All Fields]) OR “maternal age”[All Fields]) AND perinatal[All Fields] AND outcomes[All Fields])

11. Advanced[All Fields] AND (“maternal age”[MeSH Terms] OR (“maternal”[All Fields] AND “age”[All Fields]) OR “maternal age”[All Fields]) AND (“pregnancy outcome”[MeSH Terms] OR (“pregnancy”[All Fields] AND “outcome”[All Fields]) OR “pregnancy outcome”[All Fields])

12. “Reproductive behavior”[MeSH Terms] OR (“reproductive”[All Fields] AND “behavior”[All Fields]) OR “reproductive behavior”[All Fields] OR (“delayed”[All Fields] AND “childbearing”[All Fields]) OR “delayed childbearing”[All Fields]

Figure 1 – FLOW DIAGRAM OF INCLUDED STUDIES

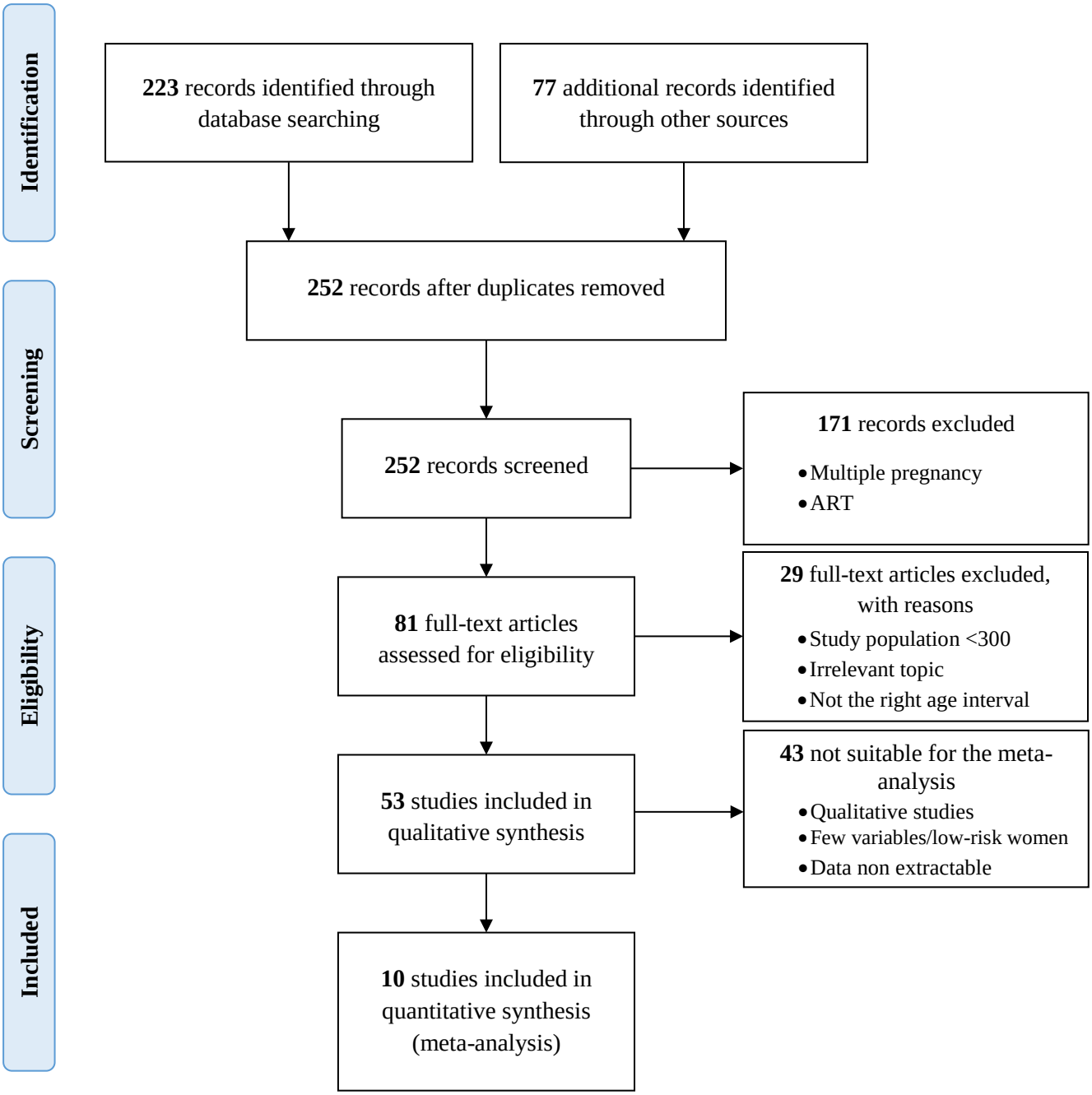

Figure 1 – Flow diagram of included studies based on the PRISMA model.(28)

ART, assisted reproductive technology

Results

A total of 252 studies were identified and after screening abstracts, 171 were considered ineligible because they included women with multiple pregnancy, assisted reproductive technology (ART) or did not address the theme (Figure 1). Eighty-one-full-text articles were integrally read and 29 dismissed due to either one of the following reasons: <300 women, different age groups or irrelevant topic. Finally, 53 studies were excluded as data had been obtained through questionnaires or were not retrievable. Ten studies met all the criteria defined for our meta-analysis. These studies were rated for quality according to the CONSORT criteria.(30) The characterization of the studies is presented in Table 1. Complete data retrieved from the studies is presented in Table 2, Table 3, Table 4, Table 5, Table 6 and Table 7.

Data on marital status were available in three out of the 10 studies. Women aged 35-40 years old (YO) were more likely to be married, compared to women 20-34 YO ones (OR 1.46; 95%CI; 1.41–1.51, I^2=90%) and >40 YO (OR 0.72; 95%CI; 0.69–0.76, I^2=90%). Compared to 35-40-year-olds, women aged 20-34 YO (OR 0.75; 95%CI; 0.73–0.77, I^2=96%) and >40 YO (OR 1.13; 95%CI; 1.08–1.18, I^2=45%) were more often smokers, as five studies showed (Figure 2). Education data were available in six out of the 10 studies. The 35-40 YO age group had >12 years of education relative to 20-34 YO (OR 1.39; 95%CI; 1.36–1.42, I^2=94%) and >40 YO age groups (OR 0.88; 95%CI; 0.85–0.91, I^2=83%) (Figure 3). On the opposite, women aged 20-34 YO (OR 0.72; 95%CI; 0.71–0.73, I^2=93%), and >40 YO (OR 1.11; 95%CI; 1.08–1.15, I^2=92%) had ≤12 years of education.

There were three studies with data on low (<18.5) and normal (18.5–24.9) body mass index (BMI). Women aged 20-34 YO had lower BMI (<18.5) relative to 35-40 YO (OR 0.52; 95%CI; 0.50–0.55, I^2=98%), and the comparison between 35-40 and >40 YO was not statistically significant (p=0.11). The younger groups (20-34 YO (OR 0.85; 95%CI; 0.84–

0.86, I^2=97%), and 35-40 YO (OR 0.88; 95%CI; 0.86–0.90, I^2=49%)) had more frequently a normal BMI. Five out of the 10 studies were available for BMI≥25 analysis, showing AMA women (35-40 YO (OR 1.18; 95%CI; 1.16–1.20, I^2=98%) and >40 YO (OR 1.09; 95%CI; 1.06–1.12, I^2=77%)) more likely to be overweight or obese (Figure 4).

Two and three studies had data on chronic and gestational hypertension, respectively. AMA women (35-40 YO (OR 1.85; 95%CI; 1.74–1.96, I^2=53%), (OR 1.07; 95%CI; 1.03–1.11, I^2=90%), and >40 YO (OR 1.65; 95%CI; 1.52–1.80, I^2=0%), (OR 1.30; 95%CI; 1.23–1.37, I^2=7%)) had more comorbidities (Figure 5). Again, women in the older groups were more likely to have pregestational (35-40 YO (OR 1.98; 95%CI; 1.84–2.12, I^2=67%), and >40 YO (OR 1.26; 95%CI; 1.13–1.40, I^2=17%)) and gestational diabetes (35-40 YO (OR 1.87; 95%CI; 1.80–1.95, I^2=98%), and >40 YO (OR 1.38; 95%CI; 1.31–1.46, I^2=0%)) as two studies showed (Figure 6).

Four studies had data on labour (spontaneous and induced) and vaginal delivery and six on elective cesarean sections (CS); women aged 20-34 YO (OR 0.75; 95%CI; 0.74–0.75, I^2=100%), (OR 0.57; 95%CI; 0.56–0.58, I^2=100%) and 35-40 YO (OR 0.77; 95%CI; 0.75–0.78, I^2=99%), (OR 0.74; 95%CI; 0.72–0.75, I^2=98%) had more spontaneous labours and vaginal deliveries. AMA women aged 35-40 YO (OR 1.12; 95%CI; 1.11–1.13, I^2=100%), (OR 2.01; 95%CI; 1.98–2.05, I^2=100%) and >40 YO (OR 1.17; 95%CI; 1.14–1.20, I^2=96%), (OR 1.38; 95%CI; 1.34–1.42, I^2=97%) had more induced labours (Figure 7) and elective CS (Figure 8, Figure 9).

Regarding maternal morbidity and mortality, two studies were available. AMA women were at higher risk of maternal near miss (35-40 YO (OR 2.02; 95%CI; 1.80–2.26, I^2=0%), and >40 YO (OR 1.76; 95%CI; 1.47–2.11, I^2=0%)) and maternal death (35-40 YO (OR 1.61; 95%CI; 1.21–2.13, I^2=0%) and >40 YO (OR 1.67; 95%CI; 1.07–2.63, I^2=0%)) (Figure 10).

Seven studies were available for preterm birth analysis. AMA women had more preterm deliveries than younger women (35-40 YO (OR 1.23; 95%CI; 1.21–1.25, I^2=88%), and >40 YO (OR 1.17; 95%CI; 1.14–1.21, I^2=74%)) (Figure 11, Figure 12).

Data on birthweight were available in three out of the 10 studies. AMA women had more babies with very low (<1500g) (35-40 YO (OR 1.25; 95%CI; 1.17–1.33, I^2=0%) and >40 YO (OR 1.19; 95%CI; 1.10–1.29, I^2=0%)) and low (1500–2500g) birthweights (35-40 YO (OR 1.10; 95%CI; 1.05–1.15, I^2=29%) and >40 YO (OR 1.35; 95%CI; 1.25–1.47, I^2=41%)) (Figure 13, Figure 14). Age group 35-40 YO had more macrosomic babies (>4000g) (OR 1.19; 95%CI; 1.15–1.23, I^2=94%) comparatively to 20-34 YO and the result 35-40 *vs.* >40 YO was not statistically significant p=0.84. Two studies had data on small for gestational age (SGA) infants. Babies born to 20-34 YO (OR 0.78; 95%CI; 0.74–0.81, I^2=0%) and >40-year-old mothers (OR 1.13; 95%CI; 1.03–1.24, I^2=75%) were more likely to be SGA (Figure 15).

Data on Neonatal Intensive Care Unit (NICU) admission and Apgar score were available in two and four out of 10 studies, respectively. New-borns of AMA women had more NICU admissions (35-40 YO (OR 1.13; 95%CI; 1.10–1.17, I^2=47%), and >40 YO (OR 1.20; 95%CI; 1.13–1.27, I^2=0%)) and Apgar scores <7 at 5 minutes (35-40 YO (OR 1.31; 95%CI; 1.27–1.35, I^2=95%), and >40 YO (OR 1.16; 95%CI; 1.08–1.24, I^2=66%)) (Figure 16).

Regarding perinatal mortality and stillbirth, data were available in six and five out of 10 studies, respectively. AMA women had higher rates of perinatal mortality (35-40 YO (OR 1.27; 95%CI; 1.20–1.33, I^2=74%), and >40 YO (OR 1.33; 95%CI; 1.21–1.46, I^2=55%)) (Figure 17, Figure 18) and stillbirth (35-40 YO (OR 1.60; 95%CI; 1.53–1.68, I^2=83%), and >40 YO (OR 1.33; 95%CI; 1.21–1.46, I^2=32%)).

Discussion

Out of the three age groups, 35-40-year-old women were more likely to be married. This is in disagreement with other studies that almost consistently showed the older group composed of married women,(5, 14) but it could partially be explained by the "patchwork families" concept: divorced women who had a child with their second partner, not necessarily their husband.(3, 12) Moreover, despite previous references about older women being more responsible,(17, 31) women 40+ were more frequently smokers compared to 35-40-year-old women.

Whether older pregnant women have more (3, 14, 20) or less (32) schooling greatly depends on the country of assessment, the study period and the concept of higher education. In our analysis, we found women 35-40 years old to be higher educated (>12 years of schooling) compared to the other groups (20-34 and >40). The majority of studies, after adjusting for education and other confoundable factors, still registered significant adverse outcomes.(19, 33-36) Nevertheless, some authors claim that education could be a mitigating factor of maternal age on neonatal outcomes.(18, 20, 22, 32)

Consistently with previous studies,(4, 17, 37) in our meta-analysis the younger groups had a normal body mass index (BMI) and as age progressed women tended to be overweight or obese (BMI≥25). A higher BMI is considered an important predisposing factor towards the incidence of diabetes mellitus and gestational diabetes and hypertension.(17, 38)

In our meta-analysis, chronic hypertension and gestational hypertension, pre-gestational diabetes and gestational diabetes were more frequent among the older age groups, which goes accordingly to the majority of studies.(5, 17, 31, 38-40) Advanced maternal age (AMA) is a risk factor for gestational diabetes, as pancreatic B-cell function and insulin sensitivity fall with age.(10, 18) Some authors blame these co-morbidities for the adverse outcomes in older pregnant women.(13, 15) Notwithstanding, studies that only included low-risk pregnant

women without any previous condition still found worse outcomes in the AMA group. As so, pre-existing disease does not fully explain adverse events associated with age.(5, 18) Also, some authors suggest adjusting for these variables would not always be accurate; as such co-morbidities are likely to be caused by older age (and are therefore intermediate variables).(21, 24, 41)

When analysing spontaneous *vs.* induced labour, we concluded that the younger groups had more spontaneous labour and vaginal deliveries and women aged 35-39 and >40 years were more likely to not have laboured prior to birth and to be induced, similarly to previous findings.(31, 38) Women 35 years and older also had more elective cesarean sections (CS), which is consistent with the literature.(13, 31, 38, 40) Some defend that the higher incidence of induced labour in AMA pregnant women could be responsible for the higher rates of cesarean sections (CS)(18), but a recent meta-analysis (including singleton and multiple pregnancies) concluded that induction of labour in women of AMA had no statistically significant effect on CS rates;(42) the increase is therefore likely to be the result of combination of physiological changes with maternal age and an expression of physician and maternal preferences.

Older pregnant women are frequently labelled as “higher risk” (even those without known risk factors), especially when the pregnancy is a product of assisted reproductive technology, and this generalization lowers the clinical threshold for obstetrical interventions, resulting in increased rates of CS for non-medical reasons.(8, 13, 18, 25) Furthermore, chronic diseases and certain maternal characteristics associated with age (high BMI, preeclampsia and gestational diabetes) are also known to play a role.(36, 38) Finally, two large studies (36, 43) still found higher CS rates after adjustment for several maternal characteristics (even though one of them was a meta-analysis including multiple pregnancy)(36), suggesting AMA as a risk factor for cesarean birth and hypothesizing yet a biological basis for these findings: poor

progression and longer duration of labour with advancing age, impairment of myometrial contractility and dystocia are the most frequently discussed reasons.(10, 36, 43)

We found higher maternal death (MD) and maternal near miss (MNM) rates in the older groups (35-40, >40). There is very little evidence on MD and MNM in women of AMA, likely due to the low incidence of these outcomes in higher-income countries.(2) Nonetheless, two reviews (18, 39) support our findings and *Balasch and Gratacós* (39) even mention a strong tendency for increasing maternal mortality in older women in all developed countries. Risk factors for severe maternal morbidity and mortality are cardiovascular disease and hypertension, diabetes, obesity, placental abruption and complications from operative deliveries.(4, 44)

In our study, as maternal age increased, so did the risk of preterm birth. This has previously been reported by others,(31-33, 38, 39) but we found conflicting results in the literature: two large retrospective cohorts found older primiparas to be at higher risk of preterm birth compared to older multiparas,(17, 21) and some authors did not even find a clear association.(5, 13, 15, 19) Furthermore, it remains unclear if the correlation between AMA and prematurity is affected by socioeconomic factors.(20, 33) The ambiguous conclusions could be explained by the definition of preterm delivery, the differentiation between spontaneous preterm labour and iatrogenic preterm birth, baseline diseases and level of education of the mothers.(18, 39) The consequences are elevated risk of perinatal morbidity and mortality and a need for higher intensity neonatal care.(5, 21)

Women in the older groups (35-40 and >40 years) had more babies with very low and low birthweight (LBW) (<1500g and <2500g, respectively) which is in agreement with other published results.(32, 33, 38) A few small studies found no differences in terms of birthweight (BW) among the different age groups.(5, 14, 45) The correlation between AMA and LBW is seldom amended by socioeconomic factors and education levels.(19, 33, 41, 45)

Instead, two physiological approaches are more feasible: premature delivery and poor placental perfusion (due to the reduced cardiovascular reserve in AMA women), both can result in LBW.(18, 33)

There were more macrosomic babies (BW>4000g) to mothers aged 35-40 in comparison to 20-34-year-olds. Considering a greater incidence of diabetes, higher rates of macrosomia should be expected in babies born to >40-year-old mothers, but as *Guo et al.*(7) theorize, women diagnosed with gestational diabetes are likely to receive closer obstetric supervision and glucose monitoring, resulting in appropriate BW. Additionally, in an analysis of 510 288 births, *Swamy et al.*(41) concluded that besides age, parity and birth order are also important determinants of maternal weight and thus increased BW.

In our meta-analysis, the lowest incidence of small for gestational age (SGA) babies were in those born to mothers aged 35-40. Analysing 34 695 records of nulliparous women, *Ludford et al.*(31) reported an increased risk of SGA babies with age and described as possible causes smoking during pregnancy and low number of antenatal visits (and thus fewer opportunities to detect intrauterine growth restriction). Accurate analysis of SGA neonates is difficult due to the variability of the definition and the literature is conflicting: one study concluded that older primiparas but not multiparas are at elevated risk for SGA offspring (21) and when comparing SGA infants of <40 with ≥40-year-old mothers, a retrospective cohort found no difference between the two age groups.(17)

Most of the studies that didn't find differences between AMA and non-AMA women were small,(4, 14, 15, 45) and therefore lacked statistical power due to a minor AMA population.

The Apgar score is a good indicator of perinatal outcomes and a predictor of neonatal morbidity and neurological health.(22, 32) Neonates of older mothers had more probability of Neonatal Intensive Care Unit (NICU) admission and Apgar scores lower than 7 at 5 minutes.

This has previously been reported by others, though not always consistently among all the older age groups.(5, 21) A recent study with low-risk primiparas reported lower Apgar scores and NICU transfer to occur more often in operative deliveries.(37) Heightened anxiety and lower threshold for transfer to NICU in older mothers have been proposed as justifications.(21, 37)

We found AMA women to be at higher risk of stillbirth and perinatal death. Higher rates of stillbirth in older women is a common finding among other published studies,(26, 39, 46) irrespective of parity.(18, 21) This could be attributed to lethal congenital anomalies,(18) low utero-placental perfusion caused by poor uterine vasculature in older women, chronic diseases such as diabetes and hypertension and obesity.(1, 21, 26, 27) *Waldenström et al.*(47) found the age-related risk to be reduced in multiparous women, as a result of physiological adaptations during the first pregnancy. The same physiological explanations are valid for perinatal mortality,(10) though there is divergent evidence regarding this outcome,(13, 14, 17, 21) as it seems to be amendable by either socioeconomic advantage or absence of chronic diseases.(18, 20, 25)

Strengths and limitations

Strengths: Our studies were generally recent and very heterogeneous, being assessed in different low, medium and high income countries, which assures us a good and contemporary representation of the global population. Also, we included hospital and population-based studies, thus reducing the risk of bias selection.

Limitations: Although our primary goal was to perform a meta-analysis comparing outcomes in nulliparous with multiparous solely, most studies did not have the data separated by parity. We excluded studies that manifestly admitted women who used assisted reproductive technology (ART), but we didn't exclude the studies that didn't mention whether

pregnancies had been conceived naturally or artificially. We understand that the retrospective studies which are based on consulting medical records and birth certificates of a certain hospital may not have access to information on conception mode and probably did include women who underwent some type of infertility treatment. Nevertheless, knowing that the odds of having implantation of more than one embryo are higher through artificial conception, by excluding all multiple pregnancies we are automatically downsizing the ART population. These limitations were hardly under our control and were therefore insuperable.

Conclusions

This meta-analysis has demonstrated that women at advanced maternal age (AMA) are generally at a higher risk of adverse obstetrical and perinatal outcomes, as age progresses; women aged 35-40 had worse pregnancy outcomes than 20-34-year-olds and, likewise, the >40 years old compared to 35-40 age group.

In the broader literature, we found that some outcomes are the result of age-related comorbidities, others are a consequence of aging itself – and hence inevitable –, and a few can be partially explained by the generalization of AMA as a high-risk pregnancy among health professionals. Moreover, the majority of authors frequently adjusted the results for several confounders, which led us to believe that, though mitigated, higher risks persist with increasing age, in spite of better maternal education, social status or medical follow-up.

Therefore, AMA women should be made aware of the dangers of delaying pregnancy, even before reaching their mid 30s; a complicated pregnancy, high-risk infant and even the odds of maternal and perinatal death are never to be underestimated.

Nevertheless, acknowledging that the trend to postpone motherhood isn't about to decrease in the modern world, an optimistic and hopeful approach by the medical community is equally important. Older pregnant women should be individually assessed in terms of risk, instead of routinely being encompassed in a "high-risk" group, which leads to mother anxiety and biased decisions by the obstetrician. Finally, besides informing women about the possible adverse outcomes that expectedly come with maternal age, health professionals should also allow them to believe that the majority of pregnancies at AMA are successful, thus encouraging women to seek the silver linings of older motherhood; wisely using their resources, maturity and knowledge in favour of the best healthy lifestyle and appropriate obstetric surveillance.

Agradecimentos

À Doutora Ana Luísa Areia, pela disponibilidade, acompanhamento constante e motivação durante todas as fases desta dissertação.

À Prof.ª Doutora Anabela Mota Pinto, pelo desafio de elaborar este artigo científico e pelo voto de confiança.

À Dra. Helena Donato, pelo apoio dado durante a pesquisa e referenciação bibliográficas.

À Mãe e ao Pai, sempre presentes no meu percurso e crescimento académicos.

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Legends of Tables and Figures

Supplemental files

Table 1 – CHARACTERIZATION OF THE STUDIES INCLUDED IN THE META-ANALYSIS

REFERENCE	DESCRIPTION	RESULTS
Blomberg et al., 2014 *"Impact of maternal age on obstetric and neonatal outcome with emphasis on primiparous adolescents and older women: a Swedish Medical Birth Register Study"*(48)	• Population-based cohort study including **789 674 primiparous women** aged 25 years or older; • Using the **Swedish** Medical Birth Register, 1992 – 2010.	• Older women (≥30 years) revealed significantly ↑ risk of **cesarean section**, **prematurity**, **preeclampsia** and unfavourable neonatal outcomes.
Kenny et al., 2013 *"Advanced maternal age and adverse pregnancy outcome: evidence from a large contemporary cohort"*(24)	• Population-based cohort study; • Data on **215 344** singleton births in 2004 – 2008, **UK**.	• Women aged 40+ ↑ risk of **stillbirth, preterm birth, macrosomia**, and **cesarean delivery**.
Laopaiboon et al., 2014 *"Advanced maternal age and pregnancy outcomes: a multicountry assessment"*(2)	• Secondary analysis of data of the WHO Multicountry Survey on Maternal and Newborn Health; • **276 291** singleton pregnancies in 29 countries in **Africa, Asia, Latin America, and the Middle East**, 2010 – 2011.	• AMA significantly ↑ risk of maternal adverse outcomes, including **maternal near miss** and **maternal death**, as well as the risk of stillbirths and perinatal mortalities.
Mutz-Dehbalaie et al., 2013 *"Perinatal mortality and advanced maternal age"*(49)	• Retrospective cohort study; • Including **56 517** deliveries of women aged ≥25 years; • **Austria**, 1999 – 2008.	• **No significant differences** in **neonatal mortality rates** between the age groups; women >40 years ↑ risk for stillbirth.

Pasupathy et al., 2010 *"Advanced maternal age and the risk of perinatal death due to intrapartum anoxia at term"*(50)	• Retrospective cohort study; ≥25-year-old mothers; • **1 043 002** term infants with cephalic presentation; • **Scotland**, 1985 – 2004; • Excluded: antepartum stillbirth, perinatal death due to congenital abnormality or rhesus isoimmunisation and deliveries outside 37-43 weeks gestation.	• AMA ↑ risk of death due to intrapartum anoxia at term.
Richards et al., 2016 *"Primary cesarean section and adverse delivery outcomes among women of very advanced maternal age"*(35)	• Population-based cohort study; • Including **78 880** births to mothers ≥25 years; • Washington State, **USA**, 2003 – 2012; • Excluded: women with a **prior cesarean section**.	• Risk of **primary cesarean section** ↑ with age regardless of prior vaginal birth; no differences between primiparous and multiparous women.
Timofeev et al., 2013 *"Obstetric complications, neonatal morbidity, and indications for cesarean delivery by maternal age"*(51)	• Retrospective analysis of electronic medical records • **203 517** pregnancies at ≥23 gestational weeks, of women aged 25 years and older; • **Colombia**, 2002 – 2008.	• Neonates born to women aged 25-29 years had the lowest risk of birthweight <2500g, admission to NICU and perinatal mortality; • **Hypertensive disorders of pregnancy** were higher in women aged 35+ years or older.
Waldenström et al., 2014 *"Adverse pregnancy outcomes related to advanced maternal age compared with smoking and being overweight"*(52)	• A population-based register study; • Including **955 804 nulliparous** women ≥25 years; • In **Sweden and Norway**, 1990 – 2010.	• ↑ Risk of **fetal death** in 30-34-year-old age group; • Maternal age ≥30 years was associated with the same number of additional cases of fetal deaths as overweight or obesity.

Oliveira Jr et al., 2014 *"Severe maternal morbidity and maternal near miss in the extremes of reproductive age: results from a national cross- sectional multicenter study"*(44)	• Cross-sectional multicenter study; • **82 144** deliveries, women aged <50 years; • 27 obstetric units in **Brazil**, 2009 – 2010.	• ↑ **Maternal mortality** with age; older age was identified as an independent risk factor for severe maternal outcome.
Delpisheh et al., 2008 *"Pregnancy late in life: a hospital-based study of birth outcomes"*(53)	• A hospital-based data analysis; • **9506** delivery records from 2003, **UK**; • Excluded: women with diabetes, eclampsia and preeclampsia.	• Pregnancy in older women is associated with adverse birth outcomes (**low birthweight** and **very preterm birth**) particularly in primigravidas.

AMA, Advanced maternal age;

NICU, Neonatal Intensive care unit

Table 2 – Maternal Social and Obstetric Characteristics by Age Group

Variables	Total			Nulliparous			Multiparous			Married			Smoking		
Studies	**20-34**	**35-40**	**>40**	**20-34**	**35-40**	**>40**	**20-34**	**35-40**	**>40**	**20-34**	**35-40**	**>40**	**20-34**	**35-40**	**>40**
Blomberg et al., 2014	692 669	63 163	10 634	692 669	63 163	10 634	0	0	0	–	–	–	70 322	5287	958
Kenny et al., 2013	184 678	33 966	7066	69 868	8077	1558	114 810	25 889	5508	–	–	–	14 319	1732	444
Laopaiboon et al., 2014	238 504	29 245	8542	83 220	2773	845	155 284	26 472	7696	216 712	27 239	7604	–	–	–
Mutz-Dehbalaie et al., 2013	43 313	10 932	2272	–	–	–	–	–	–	–	–	–	4523	996	209
Pasupathy et al., 2010	842 966	96 870	14 953	358 674	22 608	2965	484 100	74 156	11 925	–	–	–	–	–	–
Richards et al., 2016	40 068	18 991	19 821	15 774	5971	5603	24 324	13 020	14 218	31 540	16 137	16 156	2916	860	1013
Timofeev et al., 2013	153 206	24 351	6322	64 093	6434	1595	89 113	17 917	4727	–	–	–	10 492	1232	378
Waldenström et al., 2014	845 602	94 789	15 413	845 602	94 789	15 413	0	0	0	–	–	–	–	–	–
Oliveira Jr et al., 2014	57 435	6506	1815	–	–	–	–	–	–	–	–	–	–	–	–
Delpisheh et al., 2008	7452	1216	229	5919	703	98	1533	514	131	6143	1098	203	2105	297	55

Data are in absolute numbers

Table 3 – Maternal Social and Obstetric Characteristics by Age Group

Variables	Education ≤12 years			Education >12 years			BMI <18.5			BMI 18.5–24.9			BMI ≥25		
Studies	**20-34**	**35-40**	**>40**	**20-34**	**35-40**	**>40**	**20-34**	**35-40**	**>40**	**20-34**	**35-40**	**>40**	**20-34**	**35-40**	**>40**
Blomberg et al., 2014	–	–	–	–	–	–	19 006	918	133	407 334	34 439	5381	172 398	18 251	3381
Kenny et al., 2013	–	–	–	–	–	–	3979	278	63	65 922	10 577	1998	62 309	12 975	2725
Laopaiboon et al., 2014	178 246	20 182	6149	60 258	9063	2393	–	–	–	–	–	–	–	–	–
Mutz-Dehbalaie et al., 2013	26 028	5637	1113	5461	2002	440	–	–	–	–	–	–	2814	733	190
Pasupathy et al., 2010	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–
Richards et al., 2016	12 076	4230	4904	27 468	14 438	14 531	1015	395	379	17 865	8372	8253	17 112	7967	8741
Timofeev et al., 2013	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–
Waldenström et al., 2014	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–
Oliveira Jr et al., 2014	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–
Delpisheh et al., 2008	–	–	–	–	–	–	–	–	–	–	–	–	2657	565	99

Data are in absolute numbers;

BMI, Body mass index

Table 4 – Maternal Obstetric Characteristics by Age Group

Variables	Chronic hypertension			Gestational hypertension			Pregestational diabetes			Gestational diabetes			Spontaneous labour		
Studies	**20-34**	**35-40**	**>40**	**20-34**	**35-40**	**>40**	**20-34**	**35-40**	**>40**	**20-34**	**35-40**	**>40**	**20-34**	**35-40**	**>40**
Blomberg et al., 2014	–	–	–	15 102	1610	365	–	–	–	–	–	–	574 099	45 330	6261
Kenny et al., 2013	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–
Laopaiboon et al., 2014	–	–	–	–	–	–	–	–	–	–	–	–	184 792	20 888	6191
Mutz-Dehbalaie et al., 2013	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–
Pasupathy et al., 2010	–	–	–	–	–	–	–	–	–	–	–	–	633 767	71 878	10 484
Richards et al., 2016	466	370	622	1999	928	1183	238	190	270	2155	1565	2186	–	–	–
Timofeev et al., 2013	3987	1171	493	12 099	1962	662	3076	972	301	7381	2315	805	83 200	10 956	2487
Waldenström et al., 2014	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–
Oliveira Jr et al., 2014	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–
Delpisheh et al., 2008	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–

Data are in absolute numbers

Table 5 – Maternal Outcomes by Age Group

Variables	Induced labour			Vaginal birth			Elective cesarean section			Maternal near miss			Maternal death		
Studies	**20-34**	**35-40**	**>40**	**20-34**	**35-40**	**>40**	**20-34**	**35-40**	**>40**	**20-34**	**35-40**	**>40**	**20-34**	**35-40**	**>40**
Blomberg et al., 2014	73 780	10 065	2111	591 516	45 806	6407	17 457	3853	1132	–	–	–	–	–	–
Kenny et al., 2013	–	–	–	–	–	–	18 841	5755	1381	–	–	–	–	–	–
Laopaiboon et al., 2014	25 649	2708	737	171 805	18 804	5585	–	–	–	1007	243	122	207	43	20
Mutz-Dehbalaie et al., 2013	–	–	–	33 706	7770	1459	–	–	–	–	–	–	–	–	–
Pasupathy et al., 2010	208 929	24 952	4463	740 760	78 028	11 214	32 270	8300	1785	–	–	–	–	–	–
Richards et al., 2016	–	–	–	32 054	14 078	13 620	8014	4913	6201	–	–	–	–	–	–
Timofeev et al., 2013	54 415	8551	2244	111 874	14 867	3328	–	–	–	–	–	–	–	–	–
Waldenström et al., 2014	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–
Oliveira Jr et al., 2014	–	–	–	–	–	–	–	–	–	482	114	57	95	15	8
Delpisheh et al., 2008	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–

Data are in absolute numbers

Table 6 – Perinatal Outcomes by Maternal Age Group

Variables	Preterm birth (<37 weeks)			Birthweight <1500g			Birthweight 1500–2500g			Birthweight >4000g			SGA (<10th percentile)		
Studies	**20-34**	**35-40**	**>40**	**20-34**	**35-40**	**>40**	**20-34**	**35-40**	**>40**	**20-34**	**35-40**	**>40**	**20-34**	**35-40**	**>40**
Blomberg et al., 2014	49 508	5778	1156	–	–	–	–	–	–	–	–	–	–	–	–
Kenny et al., 2013	12 902	2698	564	–	–	–	–	–	–	–	–	–	16 753	2444	564
Laopaiboon et al., 2014	14 352	1964	650	–	–	–	–	–	–	–	–	–	–	–	–
Mutz-Dehbalaie et al., 2013	3252	995	287	–	–	–	–	–	–	3127	851	178	–	–	–
Pasupathy et al., 2010	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–
Richards et al., 2016	–	–	–	1501	856	1057	271	122	208	4761	2451	2595	–	–	–
Timofeev et al., 2013	17 014	3108	977	2804	571	172	11 887	2069	686	11 031	2264	574	–	–	–
Waldenström et al., 2014	52 101	7214	1338	–	–	–	–	–	–	–	–	–	–	–	–
Oliveira Jr et al., 2014	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–
Delpisheh et al., 2008	1001	210	41	219	45	11	484	96	22	–	–	–	155	19	9

Data are in absolute numbers;

SGA, Small for gestational age

Table 7 – Perinatal Outcomes by Maternal Age Group

Variables	NICU admission			Apgar score <7 at 5min			Stillbirth			Perinatal mortality		
Studies	**20-34**	**35-40**	**>40**	**20-34**	**35-40**	**>40**	**20-34**	**35-40**	**>40**	**20-34**	**35-40**	**>40**
Blomberg et al., 2014	–	–	–	9921	1274	240	2232	374	87	–	–	–
Kenny et al., 2013	–	–	–	–	–	–	–	–	–	408	77	16
Laopaiboon et al., 2014	14 498	2044	705	5887	721	288	4447	800	300	6357	1036	383
Mutz-Dehbalaie et al., 2013	–	–	–	–	–	–	134	33	18	224	59	25
Pasupathy et al., 2010	–	–	–	–	–	–	–	–	–	1280	140	44
Richards et al., 2016	–	–	–	–	–	–	–	–	–	–	–	–
Timofeev et al., 2013	18 303	3190	966	2522	505	151	628	138	46	1124	224	74
Waldenström et al., 2014	–	–	–	13 254	2083	357	3127	614	128	1691	260	52
Oliveira Jr et al., 2014	–	–	–	–	–	–	–	–	–	–	–	–
Delpisheh et al., 2008	–	–	–	–	–	–	–	–	–	–	–	–

Data are in absolute numbers;

NICU, Neonatal Intensive Care Unit

Figure 2 – Smoking (35-40 *vs.* >40)

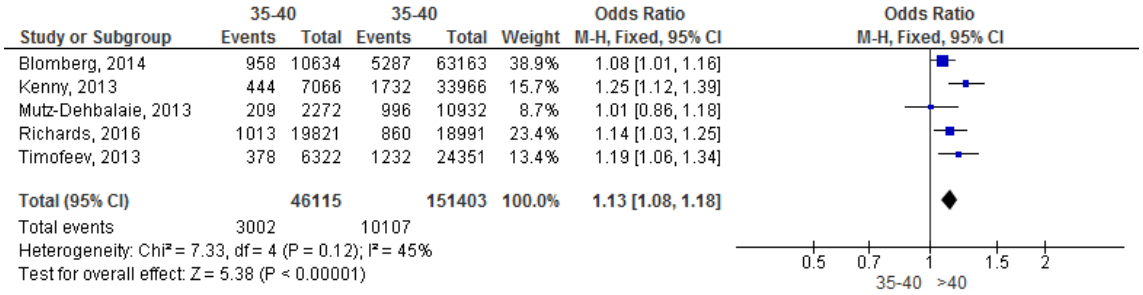

Figure 3 – Education >12 years (35-40 *vs.* >40)

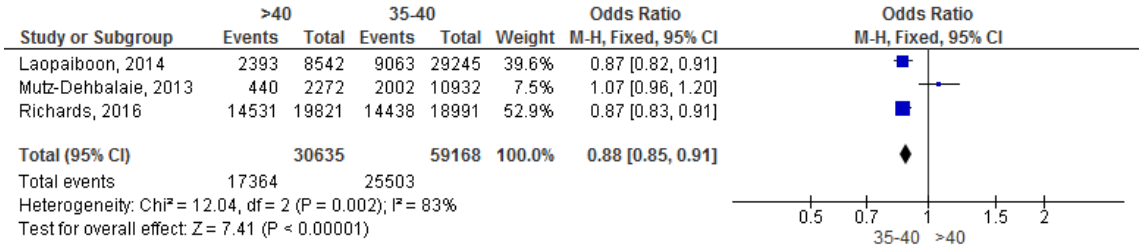

Figure 4 – Body Mass Index ≥25 (20-34 *vs.* 35-40)

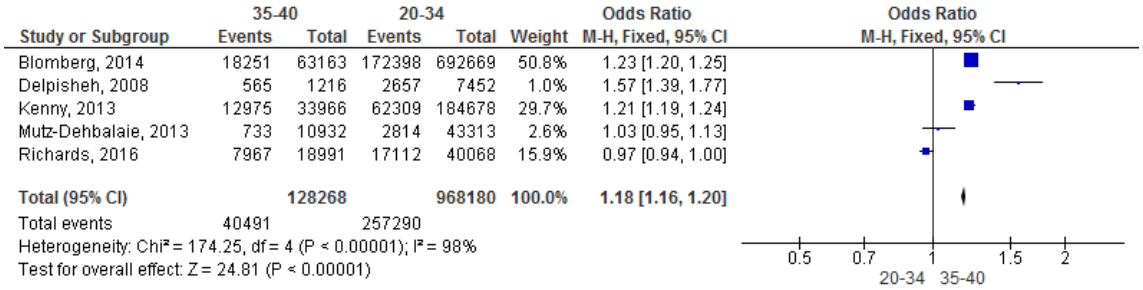

Figure 5 – Gestational Hypertension (35-40 *vs.* >40)

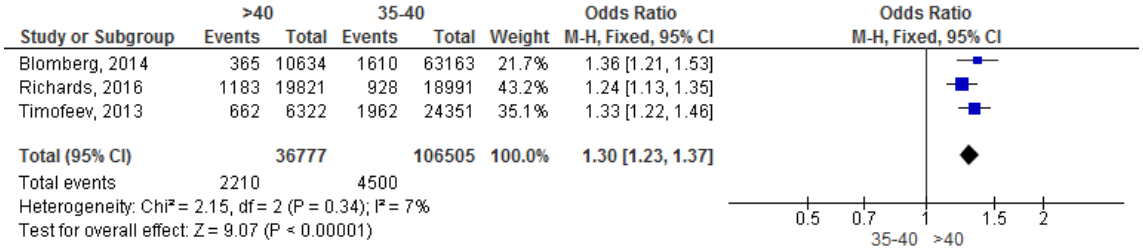

Figure 6 – Gestational Diabetes (20-34 *vs.* 35-40)

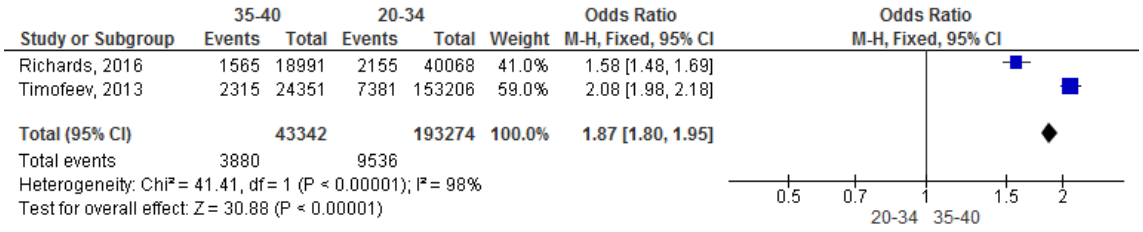

Figure 7 – Induced Labour (20-34 *vs.* 35-40)

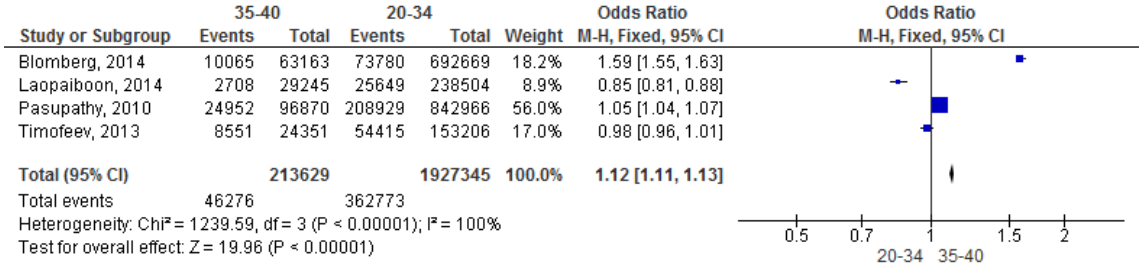

Figure 8 – Elective Cesarean Section (20-34 *vs.* 35-40)

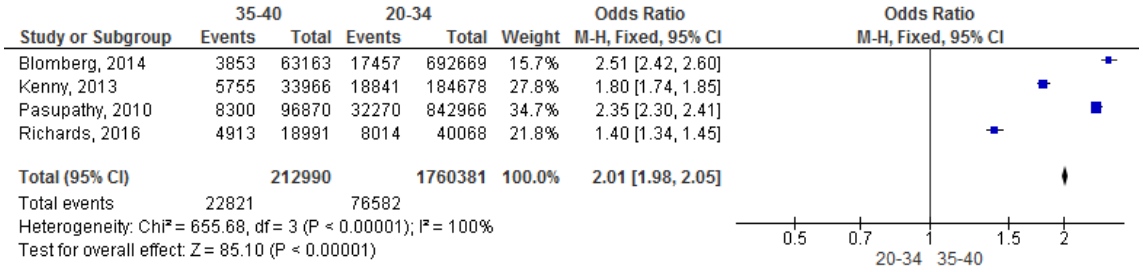

Figure 9 – Elective Cesarean Section (35-40 *vs.* >40)

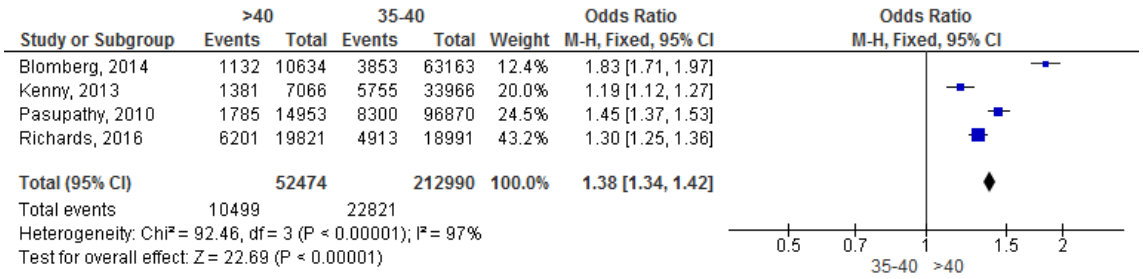

Figure 10 – Maternal Death (20-34 *vs.* 35-40)

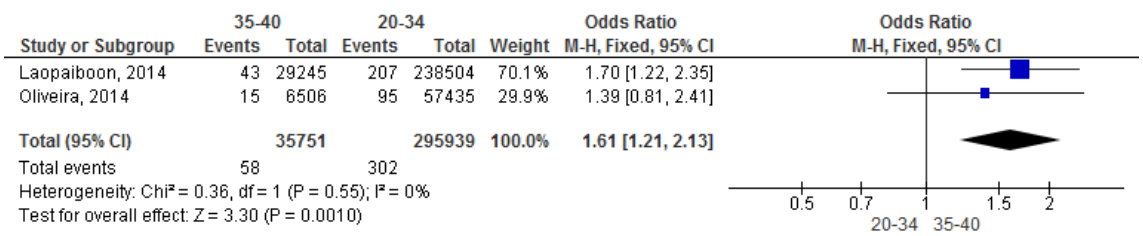

Figure 11 – Preterm Birth (<37 weeks) (20-34 *vs.* 35-40)

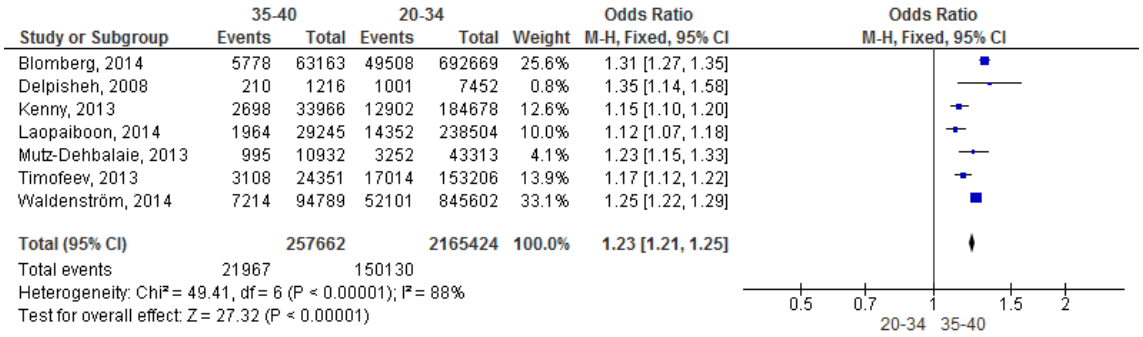

Figure 12 – Preterm Birth (<37 weeks) (35-40 *vs.* >40)

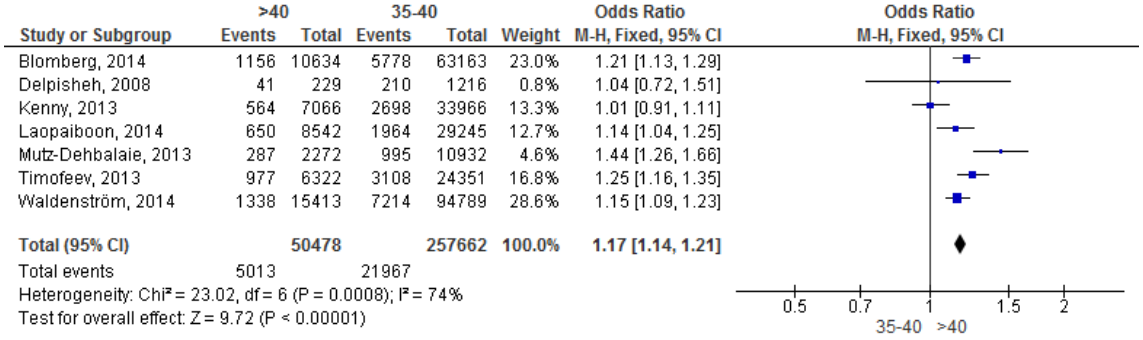

Figure 13 – Birthweight <1500g (20-34 *vs.* 35-40)

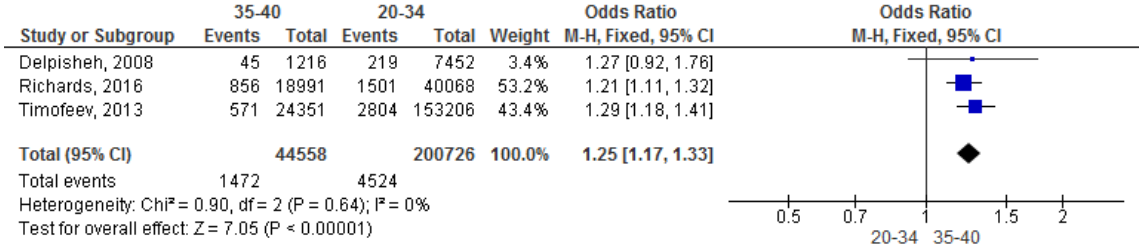

Figure 14 – Birthweight 1500–2500g (35-40 *vs.* >40)

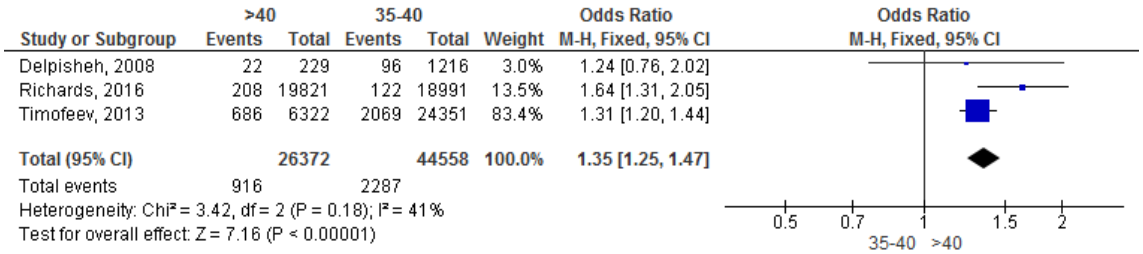

Figure 15 – Small for Gestational Age (<10th percentile) (20-34 *vs.* 35-40)

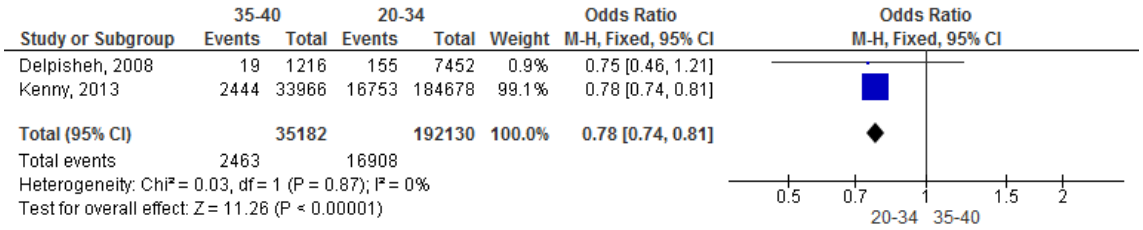

Figure 16 – Apgar score <7 at 5 minutes (35-40 *vs.* >40)

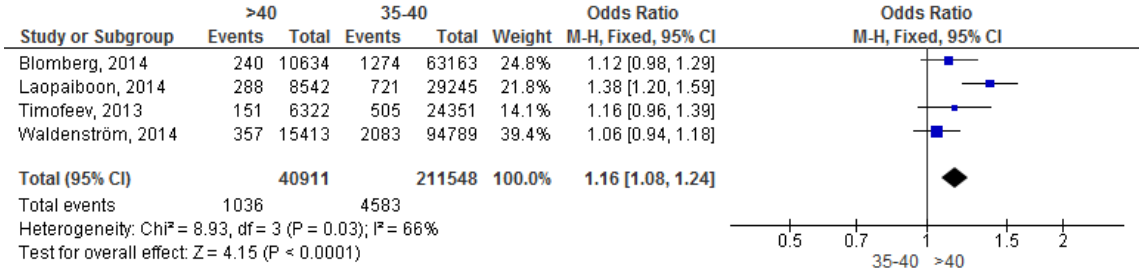

Figure 17 – Perinatal mortality (20-34 *vs.* 35-40)

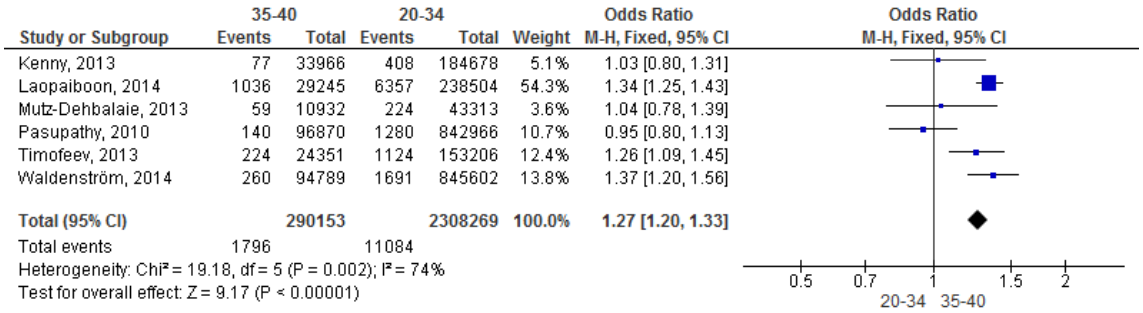

Figure 18 – Perinatal mortality (35-40 *vs.* >40)