U.PORTO
FACULDADE DE MEDICINA
UNIVERSIDADE DO PORTO

MESTRADO INTEGRADO EM MEDICINA

2021/2022

Maria Inês de Bastos Rodrigues

Impacto da Idade Materna Avançada na Morbilidade Neonatal: Revisão Sistemática / Impact of Advanced Maternal Age on Neonatal Morbidity: A Systematic Review

Março, 2022

FMUP

U.PORTO

FACULDADE DE MEDICINA
UNIVERSIDADE DO PORTO

Maria Inês de Bastos Rodrigues

Impacto da Idade Materna Avançada na Morbilidade Neonatal: Revisão Sistemática / Impact of Advanced Maternal Age on Neonatal Morbidity: A Systematic Review

Mestrado Integrado em Medicina

Área: Medicina Clínica

Tipologia: Dissertação

Trabalho efetuado sob a Orientação de:

Doutora Maria Inês Ferreira Águeda de Azevedo

E sob a Coorientação de:

Dr. Gustavo Marcondes Duarte Rocha

Trabalho organizado de acordo com as normas da revista:
The Journal of Maternal-Fetal & Neonatal Medicine

Março, 2022

FMUP

UC Dissertação/Projeto (6º Ano) - DECLARAÇÃO DE INTEGRIDADE

Eu, Maria Inês de Bastos Rodrigues, abaixo assinado, nº mecanográfico 201506066, estudante do 6º ano do Ciclo de Estudos Integrado em Medicina, na Faculdade de Medicina da Universidade do Porto, declaro ter atuado com absoluta integridade na elaboração deste projeto de opção.

Neste sentido, confirmo que **NÃO** incorri em plágio (ato pelo qual um indivíduo, mesmo por omissão, assume a autoria de um determinado trabalho intelectual, ou partes dele). Mais declaro que todas as frases que retirei de trabalhos anteriores pertencentes a outros autores, foram referenciadas, ou redigidas com novas palavras, tendo colocado, neste caso, a citação da fonte bibliográfica.

Faculdade de Medicina da Universidade do Porto, 20/03/2022

Assinatura conforme cartão de identificação:

Mª Inês B. Rodrigues

U.PORTO
FMUP FACULDADE DE MEDICINA
UNIVERSIDADE DO PORTO

UC Dissertação/Projeto (6º Ano) – DECLARAÇÃO DE REPRODUÇÃO

NOME

Maria Inês de Bastos Rodrigues

NÚMERO DE ESTUDANTE | E-MAIL

201506066	inesrodrigues116c@gmail.com

DESIGNAÇÃO DA ÁREA DO PROJECTO

Medicina Clínica

TÍTULO DISSERTAÇÃO/~~MONOGRAFIA~~ (riscar o que não interessa)

Impacto da Idade Materna Avançada na Morbilidade Neonatal: Revisão Sistemática / Impact of Advanced Maternal Age on Neonatal Morbidity: A Systematic Review

ORIENTADOR

Maria Inês Ferreira Águeda de Azevedo

COORIENTADOR (se aplicável)

Gustavo Marcondes Duarte Rocha

ASSINALE APENAS UMA DAS OPÇÕES:

É AUTORIZADA A REPRODUÇÃO INTEGRAL DESTE TRABALHO APENAS PARA EFEITOS DE INVESTIGAÇÃO, MEDIANTE DECLARAÇÃO ESCRITA DO INTERESSADO, QUE A TAL SE COMPROMETE.	☐
É AUTORIZADA A REPRODUÇÃO PARCIAL DESTE TRABALHO (INDICAR, CASO TAL SEJA NECESSÁRIO, Nº MÁXIMO DE PÁGINAS, ILUSTRAÇÕES, GRÁFICOS, ETC.) APENAS PARA EFEITOS DE INVESTIGAÇÃO, MEDIANTE DECLARAÇÃO ESCRITA DO INTERESSADO, QUE A TAL SE COMPROMETE.	☐
DE ACORDO COM A LEGISLAÇÃO EM VIGOR, (INDICAR, CASO TAL SEJA NECESSÁRIO, Nº MÁXIMO DE PÁGINAS, ILUSTRAÇÕES, GRÁFICOS, ETC.) NÃO É PERMITIDA A REPRODUÇÃO DE QUALQUER PARTE DESTE TRABALHO.	☒

Faculdade de Medicina da Universidade do Porto, 20/03/2022

Assinatura conforme cartão de identificação: Mª Inês B. Rodrigues

Dedicatória

À minha família pelo apoio incondicional e às minhas amigas que percorreram este caminho ao meu lado. Obrigada por me ajudarem a acreditar em sonhos e a ver a magia todos os dias.

"We keep moving forward, opening new doors and doing new things, because we're curious and curiosity keeps leading us down new paths."

-Walt Disney

Impact of advanced maternal age on neonatal morbidity: a systematic review

Inês Rodrigues[a]*, Henrique Soares, MD[a,b], Gustavo Rocha, MD[b], Inês Azevedo, PhD[a,b]

[a]*Faculty of Medicine, University of Porto, Porto, Portugal;* [b]*Department of Neonatology, Centro Hospitalar Universitário de São João, Porto, Portugal*

*E-mail: inesrodriguesmed@gmail.com

Impact of advanced maternal age on neonatal morbidity: a systematic review

Objective: This systematic review aimed to understand the impact of advanced maternal age (AMA) on the neonatal morbidity, based on the available scientific evidence. **Methods:** A systematic search was conducted on November 22, 2021, using the PubMed and Scopus databases to identify studies that compared the morbidity of neonates delivered to AMA mothers with that of neonates delivered to non-AMA mothers. **Results:** Sixteen studies that evaluated the effect of AMA on the neonatal morbidity were included in this review. Nine of these studies found some association between AMA and increased neonatal morbidity (with two of them only reporting an increase in asymptomatic hypoglycemia), six found no association between AMA and neonatal morbidity and one study found a decrease in morbidity in preterm neonates. The studies that found an increase in overall neonatal morbidity with AMA considered older ages for the definition of AMA, particularly ≥40 and ≥45 years. **Conclusion:** With the current evidence, it's not possible to define a clear effect of AMA on the neonatal morbidity of the delivered neonates. More studies focusing on the neonatal outcomes of AMA pregnancies are needed to better understand this topic.

Keywords: advanced maternal age; neonate; neonatal intensive care; respiratory distress syndrome; necrotizing enterocolitis; neonatal outcome

Introduction

In the most developed countries there's a trend in delayed childbearing over recent decades. [1] In these countries, advanced maternal age (AMA) became increasingly common and has been associated with a wide range of adverse obstetric, perinatal, and neonatal outcomes. [2-6]

Most of the published literature reports on the obstetric and perinatal data, with relatively few studies assessing the effect of AMA on the morbidity and mortality of the neonates resulting from these pregnancies. Higher number of perinatal complications and a higher number of admissions to neonatal intensive care units have been described in the term and near-term infants. [7] In preterm infants, especially very low birth weight

(VLBW) infants, according to some studies, AMA is associated with an increased incidence of respiratory distress syndrome, necrotizing enterocolitis, retinopathy of prematurity and periventricular leukomalacia. [8-13] On the other hand, other studies found that AMA was not associated with an increase of neonatal morbidity, or mortality, in preterm neonates. [14,15]

The objective of this systematic review was to gather all the scientific evidence on the effect of AMA on the neonatal morbidity, in order to draw conclusions and to assess the need for further studies. More specifically, this review aims to assess if neonates born to mothers of AMA present higher morbidity than those born to non-AMA mothers.

Methods

A systematic review was conducted according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines for the search, with no limit of time. PubMed and Scopus databases were systematically searched, on November 22, 2021 using the following terms: maternal age, advanced maternal age, very advanced maternal age, delayed childbearing, neonatal morbidity, neonatal outcome, pregnancy outcome, respiratory distress syndrome, transient tachypnea of the newborn, pneumothorax, bronchopulmonary dysplasia, patent ductus arteriosus, necrotizing enterocolitis, intraventricular hemorrhage, periventricular venous infarction, periventricular leukomalacia, retinopathy of prematurity, sepsis, pneumonia, meningitis, jaundice (Table 1).

After removing duplicates, two independent authors (GR and IR) screened the abstracts of 1,083 articles. Disagreements were solved upon discussion with a third element (IA). At the end of this process, 26 articles were included. After an additional search, using the same methodology for the selection process, seven more articles were included. Thus, a total of 33 articles were eligible for full-text review, after which 16 articles were included in this systematic review. The selection process flowchart can be seen in Figure 1.

All studies prior to November 22, 2021 that met the inclusion criteria were included. The inclusion criteria were studies comparing the morbidity of neonates born to mothers of advanced maternal age with that of neonates born to mothers of non-AMA. Morbidity was defined as one or more of the following outcomes: respiratory distress syndrome (RDS), pneumothorax, bronchopulmonary dysplasia (BPD), necrotizing enterocolitis (NEC), intraventricular hemorrhage (IVH), periventricular venous infarction (PVI), periventricular leukomalacia (PVL), retinopathy of prematurity (ROP), sepsis, pneumonia, meningitis, transient tachypnea of the newborn (TTN), seizures or convulsions, jaundice and any metabolic disturbance.

Exclusion criteria included: studies that included only mothers with advanced age with hypertensive disorders or diabetes; studies that only included multiple gestations; articles written in languages other than English, Portuguese, French or Spanish; studies that did not evaluate the outcomes defined for this review, namely studies that only assessed congenital anomalies. Review manuscripts were also excluded.

Data were extracted from the selected studies using a pre-determined model. Extracted data included: author name, study year(s) and country(ies), study design, sample size, maternal age ranges considered for the study, gestational ages of the included neonates, mean birth weight when available, the assessed outcomes and the main findings of the study.

Study quality assessment

The quality of the studies included in this review was assessed by two independent authors (GR and HS), using the STROBE (Strengthening the Reporting of Observational Studies in Epidemiology) [16] guidelines and a GRADE (Grading of Recommendations Assessment, Development and Evaluation) [17] level was attributed to each included article.

Results

Sixteen studies that evaluated the effect of AMA on the neonatal morbidity were included in this systematic review. A summary of the studies and their main findings can be seen in Table 2. In this set of studies, eight were retrospective cohort studies, six were retrospective case-control studies, one was a prospective case-control study, and one was a prospective cohort study. The oldest study included in this systematic review was from 1991 and the most recent was from 2021.

The studies differed in the definition of AMA. Most defined AMA as ≥ 35 or ≥40 years. Four studies assessed the neonatal outcomes of only preterm or VLBW infants, the others also included infants delivered at term.

Four of the 16 studies found an association between AMA and overall increase in neonatal morbidity [3,5,6,18], two of which considered AMA a maternal age ≥45 years and the other two considered AMA a maternal age ≥40 years. One study also found an increase in neonatal morbidity but only in twins, when comparing a maternal age ≥50 years to a maternal age of 45-49 years. [2] Other two studies found that AMA had an impact, not in the overall morbidity of the neonate, but specifically an increase in the incidence of cystic PVL [8] and RDS [13], for maternal ages ≥35 years and ≥32 years, respectively. The studies by Canto M.J. *et. al.* [19] and Romero Maldonado S. *et. al.* [20]

found an increase in the incidence of asymptomatic hypoglycemia in neonates delivered to mothers ≥40 and ≥35 years, respectively, but no increase in the overall neonatal morbidity. In the later, the increase in hypoglycemia was presumptively associated to an increased incidence of gestational diabetes mellitus in AMA pregnancies. [20]

Six of the studies found no association between AMA and neonatal morbidity, including two studies that focused only on preterm or VLBW infants. [4,15,19,21-24] Lastly, the results of one study showed that in preterm neonates, morbidity might even decrease with increasing maternal age, specifically a decreased incidence of mortality, NEC, and neonatal sepsis. [14]

Risk of bias across studies

The major biases found were: most studies had a retrospective design; AMA definition was not uniformly used in all studies; definitions of the neonatal morbidities were different among the various studies and lack of definitions of the outcomes were found in some studies; the main objective of some studies was not to evaluate specific morbidities of the newborn; different epochs and countries across the different studies including some old articles not translating the current neonatal practices; most studies did not analyze all neonatal outcomes, and some articles analyzed only one or two outcomes.

Discussion

There are several studies and meta-analysis showing that a wide range of adverse obstetrical and perinatal outcomes are associated with women of AMA. [7,25-32] Most of the adverse outcomes can be explained through the physio-pathological changes due to aging in the female reproductive system and aging-associated comorbidities. But AMA can also be an independent risk factor according to current evidence. [32]

This systematic review aimed to gather all the scientific evidence on the effect of AMA on the neonatal morbidity and mortality, more specifically, to assess if neonates born to mothers of AMA present higher prevalence of morbidities, during the neonatal period, than those born to non-AMA mothers.

Respiratory distress syndrome

RDS occurs mainly in very preterm infants with immature lungs and surfactant deficiency, and is the is the most common cause of respiratory failure in preterm infants. [33]

In this systematic review, 11 studies evaluated the impact of AMA on the incidence of RDS. The study of Dani C. *et. al.* [13] that included 63,537 newborns and compared a maternal age ≥32 years to a maternal age <32 years, concluded that AMA was a risk factor for RDS. Shrim A. *et. al.* [18] included 1,108 neonates and found that a maternal age ≥40 years was associated with higher incidence of RDS when comparing with a maternal age of 20-39 years. The study by Çetin O. *et. al.* [5] included 989 neonates and found an increase in the incidence of RDS in neonates delivered to mothers of ≥40 years when comparing to a maternal age of 18-40 years. The other eight studies [4,8,19-24] did not find an association between AMA and RDS.

Transitory tachypnea of the newborn

TTN is a benign condition that typically appears within the first two hours of life in term and late preterm neonates and is characterized by tachypnea and signs of respiratory distress. [34] Although it is usually a self-limited condition, admission to a neonatal unit is frequently required. [35] Infants born by C-section are at risk of TTN [36] and AMA has been associated to an increase in the number of prelabor C-section. [37]

In this review, the studies by Dani C. *et. al.* [13], Romero-Maldonado S. *et. al.* [20] and Celik B.D. *et. al.* [22] evaluated the effect of AMA on the incidence of TTN and no association was found in any of the studies.

Bronchopulmonary dysplasia

BPD is a disease resulting from the interference of several prenatal and postnatal factors in the development of the lower respiratory tract of extreme preterm infants and it can lead to lifelong lung disease. [38]

In this systematic review, three studies [14,15,21] evaluated the effect of AMA on BPD and none found an association between the two.

Necrotizing enterocolitis

NEC is a gastrointestinal condition affecting mainly premature neonates that can have serious effects and for many years it has been a major cause of morbidity and mortality in NICUs worldwide. [39,40]

In this systematic review, nine studies evaluated the impact of AMA on the incidence of NEC. The study by Kanungo J. *et. al.* [14] that included 12,326 neonates with a gestational age <33 weeks, concluded that the incidence of NEC decreased by 11% as maternal age increased by five years. The study by Çetin O. *et. al.* [5] associated AMA with an increased incidence of NEC. The study by Schwartz A. *et. al.* [2] analyzed 657 neonates and compared those born to mothers ≥50 years with those born to mothers of 45-49 years and showed an increase in composite severe neonatal morbidity, including NEC, but only in twins. The other six studies [8,15,19-21,24] found no association between AMA and NEC.

Neonatal sepsis

Despite maternal intrapartum prophylaxis, which reduced its rates, early-onset sepsis (EOS) remains a severe problem, especially for preterm neonates. [41,42] Risk factors include prematurity, low birth weight, chorioamnionitis, premature prolonged rupture of membranes, resuscitation and low APGAR score. [42]

In this review, eight studies assessed the effect of AMA on the incidence of neonatal sepsis. In the study by Kanungo J. *et. al.* [14], in preterm neonates, as maternal age increased by five years, the incidence of sepsis decreased by 9%. The study by Çetin O. *et. al.* [5] showed an increase in sepsis incidence with AMA. The other six studies [4,8,19-21,24] found no association. Two studies [8,20] evaluated the effect of AMA on the incidence of pneumonia and one [8] evaluated the effect on meningitis and no association was found.

Periventricular leukomalacia and intraventricular hemorrhage

Periventricular leukomalacia (PVL) is caused by dysregulation of cerebral blood flow causing ischemia of the periventricular white matter and it is a major cause of cerebral palsy in premature neonates. [43,44] Cystic PVL (cPVL) is the most severe form of the disease. [43]

In preterm infants, particularly in extremely preterm neonates, IVH remains a clinically significant problem, increasing the risk of adverse neurological outcomes. [45]

In this review, four studies evaluated the effect of AMA on PVL. The study by Rocha G. *et. al.* [8] that included 499 neonates with a gestational age of 24-30 weeks found that a maternal age ≥35 years was associated with higher incidence of echographic cystic PVL, when compared with a maternal age <35 years. In this multicenter study, the main objective was not to assess cPVL and a confirmatory diagnosis by magnetic resonance was not performed. The other three studies [14,15,21] found no association between AMA and PVL.

Seven studies [2,8,14,15,20,21,24] assessed the effect of maternal age on IVH and only Schwartz A. *et. al.* [2] found an increase in incidence, but only in twins.

Retinopathy of prematurity

Retinopathy of prematurity (ROP) is a leading cause of childhood blindness. It only occurs in preterm infants and is caused by a proliferation of retinal blood vessels. [46]

In this review, four studies evaluated the effect of AMA in the incidence of ROP and none of them found any association. [8,14,15,21]

Asymptomatic hypoglycemia

It is common in healthy newborns to temporarily present low plasma glucose levels. [47] There is no uniform definition of neonatal hypoglycemia but it is consensual that infants at risk should have their plasma glucose concentrations measured. [47] There's a high incidence of hypoglycemia in asymptomatic neonates, although its significance is unclear. [48]

In this review, five studies evaluated the effect of AMA on asymptomatic hypoglycemia, and all found an association. The study by Romero-Maldonado S. *et. al.* [20] that included 420 neonates, showed a higher incidence of asymptomatic hypoglycemia in neonates delivered to mothers ≥35 years, when comparing to neonates born to mothers of 18-34 years. The authors associate this to the higher incidence of gestational diabetes in AMA pregnancies. The study by Canto *et. al.* [19] included 682 neonates and found higher incidence of hypoglycemia in neonates born to mothers ≥40 years compared with neonates born to mothers of 20-29 years. The study by Yogev Y. *et. al.* [3] that included 5,487 neonates found a higher incidence of metabolic complications (including hypoglycemia) in neonates delivered to mothers ≥45 years when comparing to neonates delivered to younger mothers. The study by Çetin O. *et. al.* [5] also found an association between AMA and increased incidence of asymptomatic hypoglycemia and Schwartz A. *et. al.* [2] found this association but only in twins.

Jaundice and metabolic complications

In the neonatal period, jaundice is the most common morbidity, frequently requiring intervention. [49] Another metabolic complication frequently observed in neonates is hypocalcemia, with risk factors including infants of diabetic mothers, preterm infants and perinatal asphyxia. [50]

Five studies included in this systematic review studied the effect of AMA on jaundice or other metabolic complications. The study by Yogev Y. *et. al.* [3] concluded that metabolic complications were significantly higher among neonates born to mothers ≥45 years. Çetin O. *et. al.* [5] showed that AMA was associated with higher rates of hyperbilirubinemia and hypocalcemia. The other three studies [19,20,24] found that these outcomes were not associated with AMA.

NICU admissions

A systematic review and meta-analysis by Lean S.C. *et. al.* [7] including 63 cohort studies and 12 case-control studies, reported an increase in NICU admission among infants of AMA women.

Ten of the studies included in this review evaluated the effect of maternal age on the rate of NICU admissions. The studies by Çetin O. *et. al.* [5] and Shrim A. *et. al.* [18] associated a maternal age ≥40 years with an higher rate of NICU admissions. The study by Yogev Y. *et. al.* [3] found the same association but for a maternal age ≥45 years. Schwartz A. *et. al.* [2] also found an association between the two variables, but only in twins. The other six studies [4,19,20,22-24] found no association between AMA and NICU admissions.

Mortality

Although the objective of this systematic review wasn't to evaluate the effect of AMA on neonatal mortality, seven of the included studies assessed this outcome. Shrim A. *et. al.* [18] found an increase in mortality with AMA. The other six studies [2,3,15,19,21,24] found no association between the two variables.

Overall morbidity

Overall, nine studies [2,3,5,6,8,13,18-20] in this review found some association between AMA and neonatal morbidities (with two of them only reporting an increase in asymptomatic hypoglycemia [19,20] and one only reporting a significative association in twins [2]), six studies [4,15,21-24] found no association between AMA and neonatal morbidity and one study [14] found a protective effect of AMA in preterm neonates.

The studies that found an increase in overall neonatal morbidity with AMA [3,5,6,18] considered older ages for the definition of AMA, particularly ≥40 and ≥45 years. This might suggest that higher maternal ages have a higher impact on the morbidity of the neonates. On the other hand, two of the studies that found no effect of AMA only evaluated the outcomes for preterm or VLBW infants. [15,21] Adding to the fact that the study by Kanungo *et. al.* [14] found a protective effect of maternal age on the outcomes of preterm neonates, we might theorize that the effect of AMA might be different according to gestational age.

According to these results, the relationship between maternal age and neonatal morbidity is not yet clearly understood. Despite the evidence on the effect of maternal age on maternal and perinatal outcomes [7,25-32], the studies focusing on the neonatal outcomes are not as many and the results are more heterogenous. More studies focusing on neonatal outcomes are needed to understand this effect, particularly paying attention to the role of gestational age and the cut-off of maternal age.

Strengths and limitations

There have been a lot of studies and some systematic reviews reporting the effects of maternal age on maternal and perinatal morbidity. [7,25-32] However, this systematic review focuses on neonatal outcomes and complications such as RDS, TTN, BPD, NEC, sepsis, PVL, and ROP, thus bringing some new insight into this topic.

Most of the studies included were retrospective and of moderate evidence, thus, there's a great risk of bias associated with these studies, limiting its conclusions. The fact that the studies included were quite variable in terms of what is considered AMA, the different outcomes evaluated in each study, the gestational ages included and the inclusion or not of twin pregnancies, also limited the conclusions reached in this systematic review.

Conclusion

The current evidence does not allow to draw conclusions on the effect of AMA on neonatal morbidity. More well-designed prospective studies focusing on a thorough evaluation of neonatal outcomes are needed to clarify this association.

Declaration of interest statement

The authors declare they have no conflict of interests.

References

1. OECD. SF2.3: Age of mothers at childbirth and age-specific fertility. OECD; 2021.
2. Schwartz A, Many A, Shapira U, et al. Perinatal outcomes of pregnancy in the fifth decade and beyond– a comparison of very advanced maternal age groups [Article]. Scientific Reports. 2020;10(1).
3. Yogev Y, Melamed N, Bardin R, et al. Pregnancy outcome at extremely advanced maternal age. Am J Obstet Gynecol. 2010 Dec;203(6):558.e1-7.
4. Çakmak BD, Dündar B, Türker ÜA. Perinatal outcomes of advanced and extremely advanced maternal age pregnancies [Article]. Haseki Tip Bulteni. 2019;57(4):366-371.
5. Çetin O, Verit FF, Zebitay AG, et al. Neither early nor late for becoming pregnant: Comparison of the perinatal outcomes of adolescent, reproductive age, and advanced maternal age pregnancies. Turk J Obstet Gynecol. 2015 Sep;12(3):151-157.
6. Sydsjö G, Lindell Pettersson M, Bladh M, et al. Evaluation of risk factors' importance on adverse pregnancy and neonatal outcomes in women aged 40 years or older [Article]. BMC Pregnancy and Childbirth. 2019;19(1).
7. Lean SC, Derricott H, Jones RL, et al. Advanced maternal age and adverse pregnancy outcomes: A systematic review and meta-analysis. PLoS One. 2017;12(10):e0186287.
8. Rocha G, Flor-de-Lima F, Machado AP, et al. A maternal age of 35 years and over may increase the risk for cystic periventricular leukomalacia in very preterm infants. Minerva Pediatr. 2019 Oct 11.
9. Li ML, Hsu SM, Chang YS, et al. Retinopathy of prematurity in southern Taiwan: a 10-year tertiary medical center study. J Formos Med Assoc. 2013 Aug;112(8):445-53.
10. Uchida A, Miwa M, Shinoda H, et al. Association of Maternal Age to Development and Progression of Retinopathy of Prematurity in Infants of Gestational Age under 33 Weeks. J Ophthalmol. 2014;2014:187929.
11. Wu WC, Ong FS, Kuo JZ, et al. Retinopathy of prematurity and maternal age. Retina. 2010 Feb;30(2):327-31.

12. Boo NY, Cheah IG. Risk factors associated with necrotising enterocolitis in very low birth weight infants in Malaysian neonatal intensive care units. Singapore Med J. 2012 Dec;53(12):826-31.
13. Dani C, Reali MF, Bertini G, et al. Risk factors for the development of respiratory distress syndrome and transient tachypnoea in newborn infants. Italian Group of Neonatal Pneumology. Eur Respir J. 1999 Jul;14(1):155-9.
14. Kanungo J, James A, McMillan D, et al. Advanced maternal age and the outcomes of preterm neonates: a social paradox? Obstet Gynecol. 2011 Oct;118(4):872-7.
15. Nourkami-Tutdibi N, Tutdibi E, Faas T, et al. Neonatal Morbidity and Mortality in Advanced Aged Mothers-Maternal Age Is Not an Independent Risk Factor for Infants Born Very Preterm. Front Pediatr. 2021;9:747203.
16. Cuschieri S. The STROBE guidelines. Saudi J Anaesth. 2019 Apr;13(Suppl 1):S31-s34.
17. Guyatt GH, Oxman AD, Vist GE, et al. GRADE: an emerging consensus on rating quality of evidence and strength of recommendations. Bmj. 2008 Apr 26;336(7650):924-6.
18. Shrim A, Levin I, Mallozzi A, et al. Does very advanced maternal age, with or without egg donation, really increase obstetric risk in a large tertiary center? J Perinat Med. 2010 Nov;38(6):645-50.
19. Canto MJ, Reus A, Cortés S, et al. Pregnancy outcome in a Spanish population of women beyond age 40 delivered above 32 weeks' gestation [Article]. Journal of Maternal-Fetal and Neonatal Medicine. 2012;25(5):461-466.
20. Romero-Maldonado S, Quezada-Salazar CA, López Barrera MD, et al. [Effect of risk on the child of an older mother (case-control study)]. Ginecol Obstet Mex. 2002 Jun;70:295-302.
21. Tseng KT, Peng CC, Chang JH, et al. The impact of advanced maternal age on the outcomes of very low birth weight preterm infants. Medicine (Baltimore). 2019 Feb;98(5):e14336.
22. Cakmak Celik F, Aygun C, Kucukoduk S, et al. Maternal and neonatal outcomes in advanced maternal age: a retrospective cohort study. J Matern Fetal Neonatal Med. 2017 Oct;30(20):2452-2456.
23. Haines CJ, Rogers MS, Leung DH. Neonatal outcome and its relationship with maternal age. Aust N Z J Obstet Gynaecol. 1991 Aug;31(3):209-12.

24. Miremerg H, Frig O, Rona S, et al. Is advanced maternal age associated with placental vascular malperfusion? A prospective study from a single tertiary center. Arch Gynecol Obstet. 2020 Jun;301(6):1441-1447.
25. Frick AP. Advanced maternal age and adverse pregnancy outcomes. Best Pract Res Clin Obstet Gynaecol. 2021 Jan;70:92-100.
26. Attali E, Yogev Y. The impact of advanced maternal age on pregnancy outcome. Best Pract Res Clin Obstet Gynaecol. 2021 Jan;70:2-9.
27. Khalil A, Syngelaki A, Maiz N, et al.
Maternal age and adverse pregnancy outcome: a cohort study. Ultrasound Obstet Gynecol. 2013 Dec;42(6):634-43.
28. Guarga Montori M, Álvarez Martínez A, Luna Álvarez C, et al. Advanced maternal age and adverse pregnancy outcomes: A cohort study. Taiwan J Obstet Gynecol. 2021 Jan;60(1):119-124.
29. Kahveci B, Melekoglu R, Evruke IC, et al. The effect of advanced maternal age on perinatal outcomes in nulliparous singleton pregnancies. BMC Pregnancy Childbirth. 2018 Aug 22;18(1):343.
30. Ziadeh SM. Maternal and perinatal outcome in nulliparous women aged 35 and older. Gynecol Obstet Invest. 2002;54(1):6-10.
31. Ziadeh S, Yahaya A. Pregnancy outcome at age 40 and older. Arch Gynecol Obstet. 2001 Mar;265(1):30-3.
32. Pinheiro RL, Areia AL, Mota Pinto A, et al. Advanced Maternal Age: Adverse Outcomes of Pregnancy, A Meta-Analysis. Acta Med Port. 2019 Mar 29;32(3):219-226.
33. McPherson C, Wambach JA. Prevention and Treatment of Respiratory Distress Syndrome in Preterm Neonates. Neonatal Netw. 2018 May 1;37(3):169-177.
34. Jha K, Nassar GN, Makker K. Transient Tachypnea of the Newborn. StatPearls. Treasure Island (FL): StatPearls Publishing
Copyright © 2022, StatPearls Publishing LLC.; 2022.
35. Gupta N, Bruschettini M, Chawla D. Fluid restriction in the management of transient tachypnea of the newborn. Cochrane Database Syst Rev. 2021 Feb 18;2(2):Cd011466.
36. Yurdakök M. Transient tachypnea of the newborn: what is new? J Matern Fetal Neonatal Med. 2010 Oct;23 Suppl 3:24-6.

37. Martinelli KG, Gama S, Almeida A, et al. Prelabor cesarean section: the role of advanced maternal age and associated factors. Rev Saude Publica. 2021;55:9.
38. Principi N, Di Pietro GM, Esposito S. Bronchopulmonary dysplasia: clinical aspects and preventive and therapeutic strategies. J Transl Med. 2018 Feb 20;16(1):36.
39. Rich BS, Dolgin SE. Necrotizing Enterocolitis. Pediatr Rev. 2017 Dec;38(12):552-559.
40. Hackam D, Caplan M. Necrotizing enterocolitis: Pathophysiology from a historical context. Semin Pediatr Surg. 2018 Feb;27(1):11-18.
41. Simonsen KA, Anderson-Berry AL, Delair SF, et al. Early-onset neonatal sepsis. Clin Microbiol Rev. 2014 Jan;27(1):21-47.
42. Odabasi IO, Bulbul A. Neonatal Sepsis. Sisli Etfal Hastan Tip Bul. 2020;54(2):142-158.
43. Kurimoto T, Ibara S, Kamitomo M, et al. Assessment of risk factors for cystic periventricular leukomalacia. J Obstet Gynaecol Res. 2020 Nov;46(11):2383-2389.
44. Jorch G. [Periventricular leukomalacia]. Monatsschr Kinderheilkd. 1993 Jul;141(7):567-72.
45. Leijser LM, de Vries LS. Preterm brain injury: Germinal matrix-intraventricular hemorrhage and post-hemorrhagic ventricular dilatation. Handb Clin Neurol. 2019;162:173-199.
46. Bashinsky AL. Retinopathy of Prematurity. N C Med J. 2017 Mar-Apr;78(2):124-128.
47. Stark J, Simma B, Blassnig-Ezeh A. Incidence of hypoglycemia in newborn infants identified as at risk. J Matern Fetal Neonatal Med. 2020 Sep;33(18):3091-3096.
48. Karbalivand H, Iyare A, Aponte A, et al. Hypoglycemia screening of asymptomatic newborns on the 2nd day of life. J Neonatal Perinatal Med. 2021 2021/12//.
49. Agrawal R, Aggarwal R, Deorari AK, et al. Jaundice in the newborn. Indian J Pediatr. 2001 Oct;68(10):977-80.
50. Jain A, Agarwal R, Sankar MJ, et al. Hypocalcemia in the newborn. Indian J Pediatr. 2010 Oct;77(10):1123-8.

Table 1: Queries used for search in PubMed and Scopus

PubMed search query	(“advanced maternal age” OR “AMA” OR “very advanced maternal age” OR “delayed childbearing”) AND (“neonatal morbidity” OR “neonatal outcome*” OR “pregnancy outcome*” OR “newborn morbidity” OR “newborn complication*” OR “perinatal outcome*” OR “perinatal morbidity” OR “Pregnacy outcome”[MeSH])
Scopus search query	TITLE-ABS-KEY ((“advanced maternal age” OR “AMA” OR “very advanced maternal age” OR “delayed childbearing”) AND (“neonatal morbidity” OR “neonatal outcome*” OR “pregnancy outcome*” OR “newborn morbidity” OR “newborn complication*” OR “perinatal outcome*” OR “perinatal morbidity”))
Additional search terms	• “advanced maternal age” AND (“respiratory distress syndrome” OR “RDS”) • “maternal age” AND pneumothorax • advanced maternal age AND bronchopulmonary dysplasia • advanced maternal age AND patent ductus arteriosus • advanced maternal age AND necrotizing enterocolitis • advanced maternal age AND intraventricular hemorrhage • maternal age AND periventricular venous infarction • “maternal age” AND “retinopathy of prematurity” • “maternal age” AND “periventricular leukomalacia” • “advanced maternal age” AND sepsis • “advanced maternal age” AND pneumonia • “advanced maternal age” AND meningitis • “maternal age” AND transient tachypnea of the newborn • “advanced maternal age” AND jaundice

Table 2 - Summary of findings

Study	Time Period	Study Design	GRADE	Sample Size	Maternal Age (years)	Gestational Age (weeks)	Mean Birth Weight (g)	Outcomes Evaluated	Conclusions
Haines C.J. *et. al.*, 1991, Hong Kong [23]	1985-1989	Retrospective cohort study	Moderate	22,689	<20; 20-34 (control); >35	Not mentioned	Not mentioned	RDS, necessity for intubation, seizures or intracranial hemorrhage, NICU admission	The outcome of infants born to mothers >35 years was similar to the outcome of infants born to mothers between 20 to 34 years.
Dani C. *et. al.*, 1999, Italy [13]	Feb 1, 1995 – Jan 31, 1996	Prospective cohort study	Moderate	63,537	<32 (control); ≥32	Not mentioned	Not mentioned	RDS, TTN	Maternal age ≥32 is a risk factor for RDS.
Romero-Maldonado S. *et. al.*, 2001, Mexico [20]	Jan 1999 – Dec 1999	Retrospective case-control study	Moderate	420	18-34 (control); ≥35	Not mentioned	1,790.2	NICU admission, RDS, TTN, pneumonia, pneumothorax, IVH, NEC, patent ductus arteriosus, hyperglycemia, hypoglycemia, hypocalcemia, hyperbilirubinemia, sepsis	No statistically significant differences were found in the neonatal morbidity between the two groups, except for a higher incidence of asymptomatic hypoglycemia in the AMA group.

Study	Time Period	Study Design	GRADE	Sample Size	Maternal Age (years)	Gestational Age (weeks)	Mean Birth Weight (g)	Outcomes Evaluated	Conclusions
Shrim A. *et. al.*, 2010, Canada [18]	2001-2007	Retrospective cohort study	Moderate	1,108	20-39 (control); 40-44; ≥45	Not mentioned	3,363.2	RDS, NICU admission, perinatal and neonatal mortality	Babies born to mothers ≥40 years had higher rates of RDS, NICU admission and neonatal mortality.
Yogev Y. *et. al.*, 2010, Israel [3]	2000-2008	Retrospective case-control study	Moderate	5,487	20-29; 30-39; 40-44; ≥45 (study group)	Not mentioned	Not mentioned	NICU admission, metabolic complications (including hyperbilirubinemia, hypoglycemia, hypocalcemia, and erythrocythemia), neonatal death	NICU admission and metabolic complications were significantly higher among neonates born to mothers ≥45.
Kanungo J. *et. al.*, 2011, Canada [14]	2003-2008	Retrospective cohort study	Moderate	12,326	Age groups: 15-20; 21-25; 26-30; 31-35; 36-40; 41-54	<33	1,357.1	Survival without any major morbidity; BPD; IVH grade 3 or 4; PVL; ROP stage 3, 4 or 5; NEC stage 2 or 3; neonatal sepsis	In preterm neonates, as maternal age increased by 5 years, survival without major morbidity improved by 5% and mortality, NEC and sepsis reduced by 8%, 11% and 9% respectively.

Study	**Time Period**	**Study Design**	**GRADE**	**Sample Size**	**Maternal Age (years)**	**Gestational Age (weeks)**	**Mean Birth Weight (g)**	**Outcomes Evaluated**	**Conclusions**
Canto M.J. *et. al.*, 2012, Spain [19]	Jan 2000 – Dec 2007	Retrospective cohort study	Moderate	682	20-29 (control); ≥40	≥32	3,267.8	Perinatal death, NICU admission, hypoglycemia, jaundice, RDS, sepsis, asphyxia, convulsion, NEC	Only hypoglycemia was significantly higher for the AMA group, but the neonatal outcome overall wasn´t affected by maternal age.
Çetin O. *et. al.*, 2015, Turkey [5]	Jan 1, 2007 – Jan 31, 2015	Retrospective case-control study	Moderate	910	≤18; 18-40; ≥40	Not mentioned	2,846.1	RDS, neonatal sepsis, hyperbilirubinemia, NEC, convulsions, hypoglycemia, hypocalcemia, NICU admission	AMA pregnancies were associated with an increase short-term neonatal morbidity, except for NEC incidence, which was similar between the groups.
Celik F.C. *et. al.*, 2017, Turkey [22]	Jan 1, 2008 – Aug 31, 2010	Retrospective case-control study	Moderate	254	21-35 (control); ≥40	>20	Not mentioned	NICU admission, TTN, RDS	When adjusting for confounders, maternal age wasn’t associated with neonatal morbidity.

Study	Time Period	Study Design	GRADE	Sample Size	Maternal Age (years)	Gestational Age (weeks)	Mean Birth Weight (g)	Outcomes Evaluated	Conclusions
Çakmak B.D. *et. al.*, 2019, Turkey [4]	Jun 2016 – Dec 2017	Retrospective case-control study	Moderate	1,202	<35 (control); ≥35 (subdivided in 35-40 and >40)	Not mentioned	3,100.9	RDS, sepsis, NICU admission	There was no difference in neonatal morbidities between the two groups of maternal age.
Rocha G. *et. al.*, 2019, Portugal [8]	Jan 1, 2015 – Dec 31, 2016	Retrospective cohort study	Moderate	499	<35 (control); ≥35	24-30	960.8	RDS, pneumothorax, NEC, IVH, PVI, cPVL, ROP, sepsis, pneumonia, meningitis	Maternal age ≥35 was associated with higher incidence of cPVL in preterm infants.
Sydsjö G. *et. al.*, 2019, Sweden [6]	2007-2013	Retrospective case-control study	Moderate	109,130	≤39 (control); 40-44; ≥45	Not mentioned	Not mentioned	Child's health at delivery, survival	Women ≥45 years were more likely to have an unhealthy neonate, and those infants were more likely to die within the first 4 weeks.
Tseng K.T. *et. al.*, 2019, Taiwan [21]	Aug 2010 – Nov 2014	Retrospective cohort study	Moderate	536	20-34 (control); ≥35	Not mentioned	1,068.2	RDS, NEC stage ≥2, IVH grade 3 or 4, BPD, PDA, cPVL, sepsis, ROP, neonatal mortality	In VLBW infants, advanced maternal age didn't affect neonatal morbidity.

Study	**Time Period**	**Study Design**	**GRADE**	**Sample Size**	**Maternal Age (years)**	**Gestational Age (weeks)**	**Mean Birth Weight (g)**	**Outcomes Evaluated**	**Conclusions**
Miremerg H. *et. al.*, 2020, Israel [24]	Feb 2019 – Jul 2019	Prospective case-control study	Low	220	<35 (control); >35	[37-41[	3,313.0	NICU admission, sepsis, need for phototherapy, RDS, need for mechanical ventilation or support, NEC, IVH, hypoxic-ischemic encephalopathy, seizures, death	Neonatal outcomes did not differ according to maternal age.
Schwartz A. *et. al.*, 2020, Israel [2]	Jan 1, 2011 – Dec 31, 2018	Retrospective cohort study	Moderate	657	45-49 (control), ≥50	≥22	Not mentioned	Composite severe neonatal morbidity (IVH, NEC, asphyxia, perinatal death), NICU admission, hypoglycemia, ventilatory support, perinatal mortality	Neonatal outcomes are poorer for twins born to older mothers, but similar between groups of maternal age in singletons.

Study	Time Period	Study Design	GRADE	Sample Size	Maternal Age (years)	Gestational Age (weeks)	Mean Birth Weight (g)	Outcomes Evaluated	Conclusions
Nourkami-Tutdibi N. *et. al.*, 2021, Europe [15]	Apr 2011 – Jun 2012	Retrospective cohort study	Moderate	7,607	18-34 (control); 35-39; ≥40	Not mentioned	1,194.0	Infant mortality, BPD, severe brain injury (IVH ≥ grade 3 or cPVL), severe ROP, severe NEC	Adverse neonatal outcomes in very preterm infants did not differ by maternal age group.

AMA – advanced maternal age; BPD – bronchopulmonary dysplasia; IVH – intraventricular hemorrhage; NEC – necrotizing enterocolitis; NICU – neonatal intensive care unit; PDA – patent ductus arteriosus; PVI – periventricular venous infarction; (c)PVL – (cystic) periventricular leukomalacia; RDS – respiratory distress syndrome; ROP – retinopathy of prematurity; TTN – transient tachypnea of the newborn.

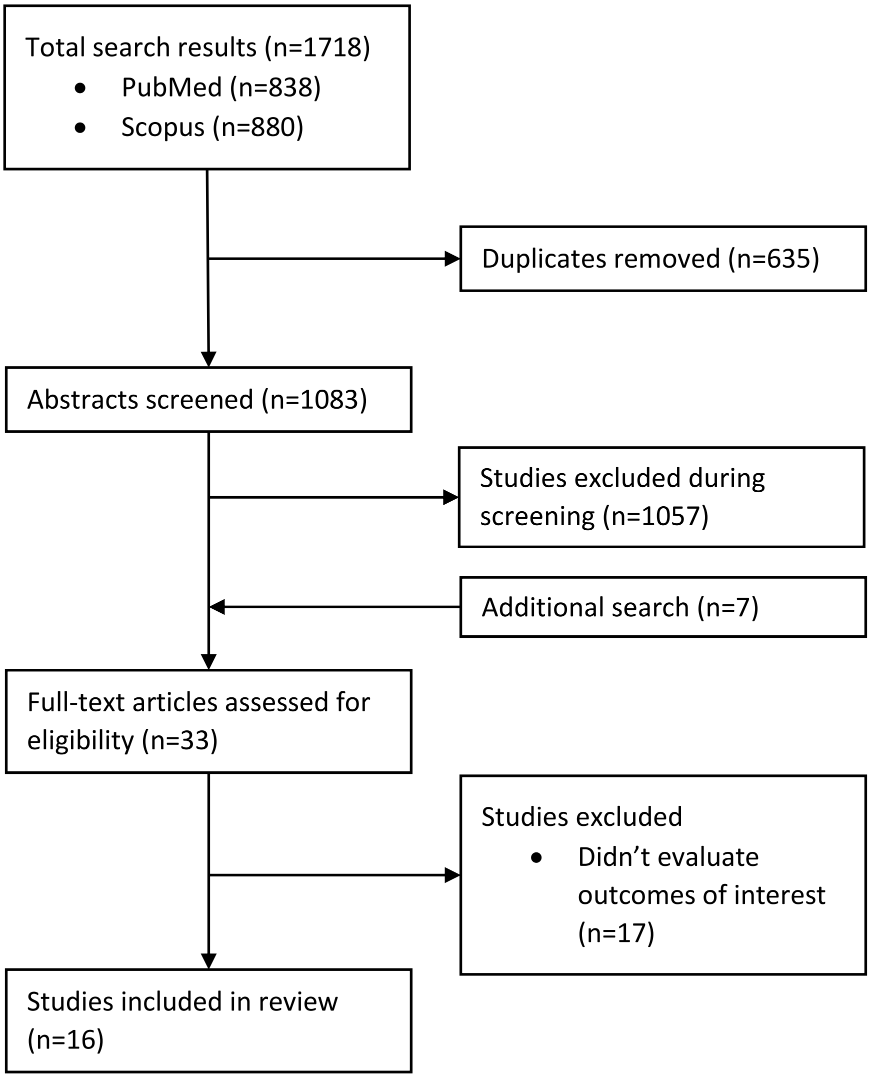

Figure 1 - PRISMA flow diagram of the selection process for the systematic review.

Apêndice 1: Reporting Guidelines - PRISMA 2009 Checklist

Section/topic	#	Checklist item	Reported on page and paragraph/ table #
TITLE			
Title	1	Identify the report as a systematic review, meta-analysis, or both. **- MANDATÓRIO**	Pág. 1, "Impact of Advanced Maternal Age and Neonatal Morbidity: A Systematic Review"
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number. **– SEGUIR RECOMENDAÇÕES DA REVISTA**	Pág. 2, "Abstract"
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known. **– MANDATÓRIO** ***O rationale corresponde à justificação da importância da revisão sistemática***	Pág. 2, "Most of the published literature reports on the obstetric and perinatal data, with relatively few studies assessing the effect of AMA on the morbidity and mortality of the neonates resulting from these pregnancies."

Apêndice 1: Reporting Guidelines - PRISMA 2009 Checklist

Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS). **- MANDATÓRIO**	Pág. 3, "More specifically, this review aims to understand if neonates born to mothers of AMA have higher morbidity than those born to non-AMA mothers."
METHODS			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number. **– FACULTATIVO**	Não aplicável. Não foi criado protocolo para esta revisão.
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale. **– MANDATÓRIO** ***É altamente recomendado, de acordo com as boas práticas da Cochrane, que não sejam aplicados critérios de exclusão baseados na língua e/ou data de publicação dos estudos.***	Pág. 4, "Inclusion criteria were (…)" "Exclusion criteria included (…)"
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched. **– MANDATÓRIO** ***Em consonância com as boas práticas da Cochrane, é mandatório que se verifique pesquisa em pelo menos duas bases de pesquisa bibliográfica (idealmente, deverão ser pesquisadas duas bases generalistas e uma específica da área). No caso de revisões sistemáticas de estudos experimentais/ensaios clínicos aleatorizados, é altamente recomendado que uma das bases pesquisadas corresponda à CENTRAL ou a bases de ensaios clínicos como a ClinicalTrials.gov.*** ***Estudos de revisão da literatura em que a pesquisa decorra numa única base de dados não serão classificados como revisões sistemáticas.***	Pág. 3, "PubMed and Scopus databases were systematically searched, on November 22, 2021 (…)"
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated. **– MANDATÓRIO** ***A query de pesquisa deve ser obrigatoriamente disponibilizada. A utilização de filtros de pesquisa da***	Pág. 18, "Table 1: Queries Used

		InterTASC é altamente recomendada (https://sites.google.com/a/york.ac.uk/issg-search-filters-resource/home)	for Search in PubMed and Scopus"
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis). **– MANDATÓRIO** ***As fases de selecção dos estudos primários devem ser descritas. Em consonância com as boas práticas da Cochrane, é mandatório que o processo de selecção envolva duas fases (fase de rastreio, em que os registos são seleccionados por título e abstract, e fase de inclusão, na qual se procede à leitura integral dos full texts). Em cada uma destas fases, o processo de selecção deve mandatoriamente envolver dois investigadores actuando de forma independente.***	Pág. 3-4, "After removing duplicates, two independent authors (GR and IR) screened the abstracts of 1083 articles. (…)"
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators. **– MANDATÓRIO** ***Trata-se de descrever de que forma se procedeu à extracção de dados dos estudos primários. Em consonância com as boas práticas da Cochrane, tal processo deverá envolver dois investigadores de forma independente.***	Pág. 4, "Data were extracted from the selected studies using a pre-determined model."
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made. **– MANDATÓRIO** ***Trata-se de descrever as variáveis para as quais foi obtida informação.***	Pág. 4, "Extracted data included: (…)"
Risk of bias in individual studies / Risk of bias across studies	12/ 15	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis. **– MANDATÓRIO** ***Em todas as revisões sistemáticas, deverá existir um processo de avaliação da qualidade dos estudos primários. No caso de revisões sistemáticas de estudos experimentais/ensaios clínicos aleatorizados, a aplicação dos critérios de risco de viés (Risk of Bias) da Cochrane é altamente recomendada. No caso de revisões sistemáticas de estudos observacionais, poderão ser seguidos os critérios ROBINS ou os critérios dos National Institutes of Health (https://www.nhlbi.nih.gov/health-topics/study-quality-assessment-tools).***	Pág. 5, "Study quality assessment"
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means). **– FACULTATIVO. APENAS NECESSÁRIO SE FOR FEITA META-ANÁLISE**	Não aplicável. Não foi feita meta-análise.
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I^2) for each meta-analysis. **– FACULTATIVO. APENAS NECESSÁRIO SE FOR FEITA META-ANÁLISE**	Não aplicável. Não foi feita

Apêndice 1: Reporting Guidelines - PRISMA 2009 Checklist

			meta-análise.
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified. **– FACULTATIVO. APLICÁVEL APENAS SE FOR FEITA META-ANÁLISE**	Não aplicável. Não foi feita meta-análise.
RESULTS			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram. **– MANDATÓRIO**	Pág. 25, “Figure 1 – PRISMA flow diagram of the selection process for the systematic review.”
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations. **– MANDATÓRIO**	Págs. 19-24, “Table 1 – Summary of findings”
Risk of bias within and across studies	19/ 22	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12). **– MANDATÓRIO**	Pág. 6, “Risk of Bias Across Studies”
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot. **– FACULTATIVO. APLICÁVEL APENAS SE FOR FEITA META-ANÁLISE**	Não aplicável. Não foi feita meta-análise.
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency. **– FACULTATIVO. MANDATÓRIO APENAS SE FOR FEITA META-ANÁLISE**	Não aplicável. Não foi feita meta-análise.
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]). **– FACULTATIVO. APLICÁVEL APENAS SE FOR FEITA META-ANÁLISE**	Não aplicável. Não foi feita meta-análise.
DISCUSSION			
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers). **– MANDATÓRIO**	Pág. 12-13, “Overall morbidity” and “Strengths and

			limitations”
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias). **– MANDATÓRIO**	Pág. 13, “Strengths and Limitations”
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research. **– MANDATÓRIO**	Pág. 13, “Conclusion”
FUNDING			
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review. **– SEGUIR RECOMENDAÇÕES DA REVISTA**	Pág. 13, “Declaration of Interest Statement”

From: Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. PLoS Med 6(7): e1000097. doi:10.1371/journal.pmed1000097

For more information, visit: **www.prisma-statement.org**.

Apêndice 2: Regras de Formatação da Revista

The Journal of Maternal-Fetal & Neonatal Medicine – Instructions for Authors

(Dísponível em: https://www.tandfonline.com/action/authorSubmission?show=instructions&journalCode=ijmf20#style-guidelines)

COVID-19 impact on peer review

As a result of the significant disruption that is being caused by the COVID-19 pandemic we understand that many authors and peer reviewers will be making adjustments to their professional and personal lives. As a result they may have difficulty in meeting the timelines associated with our peer review process. Please let the journal editorial office know if you need additional time. Our systems will continue to remind you of the original timelines but we intend to be flexible.

Thank you for choosing to submit your paper to us. These instructions will ensure we have everything required so your paper can move through peer review, production and publication smoothly. Please take the time to read and follow them as closely as possible, as doing so will ensure your paper matches the journal's requirements.

For general guidance on every stage of the publication process, please visit our Author Services website.

For editing support, including translation and language polishing, explore our Editing Services website

About the Journal

The Journal of Maternal-Fetal & Neonatal Medicine is an international, peer-reviewed journal publishing high-quality, original research. Please see the journal's Aims & Scope for information about its focus and peer-review policy.

Please note that this journal only publishes manuscripts in English.

The Journal of Maternal-Fetal & Neonatal Medicine accepts the following types of article: Original Article, Review Article, Letter to the Editor.

The Journal of Maternal-Fetal & Neonatal Medicine accepts the following types of article:

- Original Articles
- Review Articles: Review articles should examine published research on topics relevant to maternal-fetal medicine. The review article should provide a critical analysis of the available information, should lead to a rational conclusion, and highlight areas of future investigation.
- Short Reports: These should be of original laboratory or clinical contributions.
- Letters to the Editor: These may offer criticism of published material in an objective, constructive and educational manner. Within these limits, Letters to the Editor may be

provocative and inducive of further debate. They may also discuss matters of general interest. The material for such can be taken from any source of information so long as it pertains to the general field of maternal-fetal medicine, newborn medicine, perinatal genetics, and perinatal ethics in the broadest sense. They will be reviewed by the appropriate editor and will be subject to editing and possible abridgement. If accepted, a copy will be sent to the author(s) of the original article referred to in the Letter to the Editor, giving the author(s) the opportunity to provide a rebuttal with new material considered for publication with the Letter to the Editor.

- Opinions and Hypotheses
- Education and Debate Articles: These are usually invited, but reports on all aspects of medicine and health are welcomed. They will be peer-reviewed, and should contain an unstructured abstract of no more than 150 words.

The Journal of Maternal-Fetal & Neonatal Medicine considers all manuscripts on the strict condition that:

- they are the property (copyright) of the submitting author(s), have been submitted only to *The Journal of Maternal-Fetal & Neonatal Medicine*,
- that they have not been published already, nor are they under consideration for publication, nor in press elsewhere.

Authors who fail to adhere to this condition will be charged all costs which The *Journal of Maternal-Fetal & Neonatal Medicine* incurs, and their papers will not be published. Copyright will be transferred to the journal *The Journal of Maternal-Fetal & Neonatal Medicine* and Informa UK Ltd., if the paper is accepted.

The Journal of Maternal-Fetal & Neonatal Medicine considers all manuscripts at the Editors' discretion; the Editors' decision is final.

In general, the Journal will not publish papers which are merely confirmatory of earlier work, or that describe relatively minor modifications of existing techniques or methods.

Co-Editors-in-Chief:

Professor Gian Carlo Di Renzo
Professor and Chairman Dept. of Ob/Gyn and Centre for Perinatal and Reproductive Medicine
Santa Maria della Misericordia University Hospital
06132 San Sisto, Perugia, Italy
Tel. +39 075 5783829, +39 075 5783231
Fax +39 075 5783829
E-mail address: giancarlo.direnzo@unipg.it

Professor Dev Maulik
UMKC School of Medicine 2411 Holmes Street Room M1-103B
Kansas City, MO 64108, USA
Tel: 816-235-1788
Fax: 816-235-6579
Email address: journalm@umkc.edu

Open Access

You have the option to publish open access in this journal via our Open Select publishing program. Publishing open access means that your article will be free to access online immediately on publication, increasing the visibility, readership and impact of your research. Articles published Open Select with Taylor & Francis typically receive 95% more citations* and over 7 times as many downloads** compared to those that are not published Open Select.

Your research funder or your institution may require you to publish your article open access. Visit our Author Services website to find out more about open access policies and how you can comply with these.

You will be asked to pay an article publishing charge (APC) to make your article open access and this cost can often be covered by your institution or funder. Use our APC finder to view the APC for this journal.

Please visit our Author Services website if you would like more information about our Open Select Program.

*Citations received up to 9th June 2021 for articles published in 2016-2020 in journals listed in Web of Science®. Data obtained on 9th June 2021, from Digital Science's Dimensions platform, available at https://app.dimensions.ai
**Usage in 2018-2020 for articles published in 2016-2020.

Peer Review and Ethics

Taylor & Francis is committed to peer-review integrity and upholding the highest standards of review. Once your paper has been assessed for suitability by the editor, it will then be single blind peer reviewed by independent, anonymous expert referees. If you have shared an earlier version of your Author’s Original Manuscript on a preprint server, please be aware that anonymity cannot be guaranteed. Further information on our preprints policy and citation requirements can be found on our Preprints Author Services page. Find out more about what to expect during peer review and read our guidance on publishing ethics.

Preparing Your Paper

All authors submitting to medicine, biomedicine, health sciences, allied and public health journals should conform to the Uniform Requirements for Manuscripts Submitted to Biomedical Journals, prepared by the International Committee of Medical Journal Editors (ICMJE).

Structure

Your paper should be compiled in the following order: title page; abstract; keywords; main text introduction, materials and methods, results, discussion; acknowledgments; declaration of interest statement; references; appendices (as appropriate); table(s) with caption(s) (on individual pages); figures; figure captions (as a list).

Word Limits

Please include a word count for your paper.

A typical paper for this journal should be no more than 3000 words

Style Guidelines

Please refer to these quick style guidelines when preparing your paper, rather than any published articles or a sample copy.

Any spelling style is acceptable so long as it is consistent within the manuscript.

Please use single quotation marks, except where 'a quotation is "within" a quotation'.

Please note that long quotations should be indented without quotation marks.

More Information About Word Limits

- Original Articles: The maximum length is 3000 words (excluding references), including headings and 600-word abstract, maximum of 2 figures and/or tables, a brief rationale and an addendum. The addendum allows to include materials, methods, statistics, references etc. Original articles should have a maximum of 50 references.
- Review articles: Review articles should examine published research on topics relevant to maternal-fetal medicine. The review article should provide a critical analysis of the available information, should lead to a rational conclusion, and highlight areas of future investigation. The maximum length is 3000 words (excluding references), including headings and max 400-word abstract, maximum of 3 figures and/or tables, and up to 30 references. Review articles should have a maximum of 50 references.
- Short Reports: These should be of original laboratory or clinical contributions. The maximum length is 1200 words (excluding references), including headings and 300-word abstract, maximum of 1 figure and/or table. The addendum allows to include materials, methods, statistics, references etc. Short reports should have a maximum of 20 references.
- Letters to the Editor: Letters to the Editor may offer criticism of published material in an objective, constructive and educational manner. Within these limits, Letters to the Editor may be provocative and inducive of further debate. They may also discuss matters of general interest. The material for such can be taken from any source of information so long as it pertains to the general field of Maternal-Fetal Medicine, Newborn Medicine, Perinatal Genetics, and Perinatal Ethics in the broadest sense. They will be reviewed by the appropriate editor and will be subject to editing and possible abridgement. If accepted, a copy will be sent to the author(s) of the original article referred to in the Letter to the Editor,

giving the author(s) the opportunity to provide a rebuttal with new material considered for publication with the Letter to the Editor. Letters to the editor should have a maximum of 20 references.

- Opinions and Hypotheses: These should be 400-600 words in length with one figure or table and a maximum of five references. Opinions and hypotheses should have a maximum of 20 references.
- Education and Debate Articles: These are usually invited and should not exceed 2000 words, but reports on all aspects of medicine and health are welcomed. They will be peer-reviewed, and should contain an unstructured abstract of no more than 150 words. Education and debate articles should have a maximum of 20 references.

Formatting and Templates

Papers may be submitted in Word format. Figures should be saved separately from the text. To assist you in preparing your paper, we provide formatting template(s).

Word templates are available for this journal. Please save the template to your hard drive, ready for use.

If you are not able to use the template via the links (or if you have any other template queries) please contact us here.

References

Please use this reference guide when preparing your paper. An EndNote output style is also available to assist you.

Taylor & Francis Editing Services

To help you improve your manuscript and prepare it for submission, Taylor & Francis provides a range of editing services. Choose from options such as English Language Editing, which will ensure that your article is free of spelling and grammar errors, Translation, and Artwork Preparation. For more information, including pricing, visit this website.

Checklist: What to Include

1. **Author details.** Please ensure everyone meeting the International Committee of Medical Journal Editors (ICMJE) requirements for authorship is included as an author of your paper. Please ensure all listed authors meet the Taylor & Francis authorship criteria. All authors of a manuscript should include their full name and affiliation on the cover page of the manuscript. Where available, please also include ORCiDs and social media handles (Facebook, Twitter or LinkedIn). One author will need to be identified as the corresponding author, with their email address normally displayed in the article PDF (depending on the journal) and the online article. Authors' affiliations are the affiliations where the research was conducted. If any of the named co-authors moves affiliation during the peer-review process, the new affiliation can be given as a footnote. Please note that no changes to affiliation can be made after your paper is accepted. Read more on authorship.

2. Should contain a structured abstract of 600 words.

   Should include the following:

   - Objective
   - Methods
   - Results
   - Conclusion

Read tips on writing your abstract.

3. **Graphical abstract** (optional). This is an image to give readers a clear idea of the content of your article. It should be a maximum width of 525 pixels. If your image is narrower than 525 pixels, please place it on a white background 525 pixels wide to ensure the dimensions are maintained. Save the graphical abstract as a .jpg, .png, or .tiff. Please do not embed it in the manuscript file but save it as a separate file, labelled GraphicalAbstract1.

4. You can opt to include a **video abstract** with your article. Find out how these can help your work reach a wider audience, and what to think about when filming.

5. Between 5 and 6 **keywords**. Read making your article more discoverable, including information on choosing a title and search engine optimization.

6. **Funding details.** Please supply all details required by your funding and grant-awarding bodies as follows:
   For single agency grants
   This work was supported by the [Funding Agency] under Grant [number xxxx].
   For multiple agency grants
   This work was supported by the [Funding Agency #1] under Grant [number xxxx]; [Funding Agency #2] under Grant [number xxxx]; and [Funding Agency #3] under Grant [number xxxx].

7. **Disclosure statement.** This is to acknowledge any financial or non-financial interest that has arisen from the direct applications of your research. If there are no relevant competing interests to declare please state this within the article, for example: *The authors report there are no competing interests to declare*. Further guidance on what is a conflict of interest and how to disclose it.

8. **Supplemental online material.** Supplemental material can be a video, dataset, fileset, sound file or anything which supports (and is pertinent to) your paper. We publish supplemental material online via Figshare. Find out more about supplemental material and how to submit it with your article.

9. **Figures.** Figures should be high quality (1200 dpi for line art, 600 dpi for grayscale and 300 dpi for colour, at the correct size). Figures should be supplied in one of our preferred file formats: EPS, PS, JPEG, TIFF, or Microsoft Word (DOC or DOCX) files are acceptable for figures that have been drawn in Word. For information relating to other file types, please

consult our Submission of electronic artwork document.

10. **Tables.** Tables should present new information rather than duplicating what is in the text. Readers should be able to interpret the table without reference to the text. Please supply editable files.
11. **Equations.** If you are submitting your manuscript as a Word document, please ensure that equations are editable. More information about mathematical symbols and equations.
12. **Units.** Please use SI units (non-italicized).

Using Third-Party Material

You must obtain the necessary permission to reuse third-party material in your article. The use of short extracts of text and some other types of material is usually permitted, on a limited basis, for the purposes of criticism and review without securing formal permission. If you wish to include any material in your paper for which you do not hold copyright, and which is not covered by this informal agreement, you will need to obtain written permission from the copyright owner prior to submission. More information on requesting permission to reproduce work(s) under copyright.

Disclosure Statement

Please include a disclosure statement, using the subheading "Disclosure of interest." If you have no interests to declare, please state this (suggested wording: *The authors report no conflict of interest*). For all NIH/Welcome-funded papers, the grant number(s) must be included in the declaration of interest statement. Read more on declaring conflicts of interest.

Clinical Trials Registry

In order to be published in a Taylor & Francis journal, all clinical trials must have been registered in a public repository, ideally at the beginning of the research process (prior to participant recruitment). Trial registration numbers should be included in the abstract, with full details in the methods section. Clinical trials should be registered prospectively – i.e. before participant recruitment. However, for clinical trials that have not been registered prospectively, Taylor & Francis journals requires retrospective registration to ensure the transparent and complete dissemination of all clinical trial results which ultimately impact human health. Authors of retrospectively registered trials must be prepared to provide further information to the journal editorial office if requested. The clinical trial registry should be publicly accessible (at no charge), open to all prospective registrants, and managed by a not-for-profit organization. For a list of registries that meet these requirements, please visit the WHO International Clinical Trials Registry Platform (ICTRP). The registration of all clinical trials facilitates the sharing of information among clinicians, researchers, and patients, enhances public confidence in research, and is in accordance with the ICMJE guidelines.

Complying with Ethics of Experimentation

Please ensure that all research reported in submitted papers has been conducted in an ethical and responsible manner, and is in full compliance with all relevant codes of experimentation and legislation. All original research papers involving humans, animals, plants, biological material, protected or non-public datasets, collections or sites, must include a written statement in the Methods section, confirming ethical approval has been obtained from the appropriate local ethics committee or Institutional Review Board and that where relevant, informed consent has been obtained. For animal studies, approval must have been obtained from the local or institutional animal use and care committee. All research studies on humans (individuals, samples, or data) must have been performed in accordance with the principles stated in the Declaration of Helsinki. In settings where ethics approval for non-interventional studies (e.g. surveys) is not required, authors must include a statement to explain this. In settings where there are no ethics committees in place to provide ethical approval, authors are advised to contact the Editor to discuss further. Detailed guidance on ethics considerations and mandatory declarations can be found in our Editorial Policies section on Research Ethics.

Consent

All authors are required to follow the ICMJE requirements and Taylor & Francis Editorial Policies on privacy and informed consent from patients and study participants. Authors must include a statement to confirm that any patient, service user, or participant (or that person's parent or legal guardian) in any type of qualitative or quantitative research, has given informed consent to participate in the research. For submissions where patients or participants can be potentially identified (e.g. a clinical case report detailing their medical history, identifiable images or media content, etc), authors must include a statement to confirm that they have obtained written informed consent to publish the details from the affected individual (or their parents/guardians if the participant in not an adult or unable to give informed consent; or next of kin if the participant is deceased). The process of obtaining consent to publish should include sharing the article with the individual (or whoever is consenting on their behalf), so that they are fully aware of the content of the article before it is published. Authors should familiarise themselves with our policy on participant/patient privacy and informed consent. They may also use the Consent to Publish Form, which can be downloaded from the same Author Services page.

Health and Safety

Please confirm that all mandatory laboratory health and safety procedures have been complied within the course of conducting any experimental work reported in your paper. Please ensure your paper contains all appropriate warnings on any hazards that may be involved in carrying out the experiments or procedures you have described, or that may be involved in instructions, materials, or formulae.

Please include all relevant safety precautions; and cite any accepted standard or code of practice. Authors working in animal science may find it useful to consult the International Association of Veterinary Editors' Consensus Author Guidelines on Animal Ethics and Welfare and Guidelines for the Treatment of Animals in Behavioural Research and Teaching. When a product has not yet been approved by an appropriate regulatory body for the use described in your paper, please specify this, or that the product is still investigational.

Submitting Your Paper

This journal uses Taylor & Francis' Submission Portal to manage the submission process. The Submission Portal allows you to see your submissions across Taylor & Francis' journal portfolio in one place. To submit your manuscript please click here.

Please note that *The Journal of Maternal-Fetal & Neonatal Medicine* uses Crossref™ to screen papers for unoriginal material. By submitting your paper to *The Journal of Maternal-Fetal & Neonatal Medicine* you are agreeing to originality checks during the peer-review and production processes.

On acceptance, we recommend that you keep a copy of your Accepted Manuscript. Find out more about sharing your work.

Publication Charges

There are no submission fees, publication fees or page charges for this journal.

Colour figures will be reproduced in colour in your online article free of charge. If it is necessary for the figures to be reproduced in colour in the print version, a charge will apply.

Charges for colour figures in print are £300 per figure ($400 US Dollars; $500 Australian Dollars; €350). For more than 4 colour figures, figures 5 and above will be charged at £50 per figure ($75 US Dollars; $100 Australian Dollars; €65). Depending on your location, these charges may be subject to local taxes.

Copyright Options

Copyright allows you to protect your original material, and stop others from using your work without your permission. Taylor & Francis offers a number of different license and reuse options, including Creative Commons licenses when publishing open access. Read more on publishing agreements.

Complying with Funding Agencies

We will deposit all National Institutes of Health or Wellcome Trust-funded papers into PubMedCentral on behalf of authors, meeting the requirements of their respective open access policies. If this applies to you, please tell our production team when you receive your article proofs, so we can do this for you. Check funders' open access policy mandates here. Find out more about sharing your work.

Accepted Manuscripts Online (AMO)

This journal posts manuscripts online as rapidly as possible, as a PDF of the final, accepted (but unedited and uncorrected) paper. This is clearly identified as an unedited manuscript and is referred to as the Accepted Manuscript Online (AMO). No changes will be made to the content of the original paper for the AMO version but, after copy-editing, typesetting, and review of the resulting proof, the final corrected version (the Version of Record [VoR]), will be published, replacing the AMO version.

The VoR is the article in its final, definitive and citable form (this may not be immediately paginated, but is the version that will appear in an issue of the journal). Both the AMO version and VoR can be cited using the same DOI (digital object identifier). To ensure rapid publication, we ask you to return your signed publishing agreement as quickly as possible, and return corrections within 48 hours of receiving your proofs.

My Authored Works

On publication, you will be able to view, download and check your article's metrics (downloads, citations and Altmetric data) via My Authored Works on Taylor & Francis Online. This is where you can access every article you have published with us, as well as your free eprints link, so you can quickly and easily share your work with friends and colleagues.

We are committed to promoting and increasing the visibility of your article. Here are some tips and ideas on how you can work with us to promote your research.

Queries

If you have any queries, please visit our Author Services website or contact us here.

Updated 16th March 2022