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ORIGINAL ARTICLE

Perinatal outcomes in pregnant women over 45 years old: Singleton or multiple pregnancy?☆

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KEYWORDS
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Abstract
Introduction: Advanced maternal age is associated with a greater number of obstetric complications and adverse perinatal outcomes. It is increasingly common to find pregnant women over 45 years of age and even over 50. There are few studies that evaluate perinatal outcomes at extreme ages, over 45 years of age. Therefore, the objective of this study is to explore perinatal outcomes in the pregnancies of women over 45, as well as to compare twin and singleton pregnancies in this population.
Material and methods: An observational retrospective case–control study was carried in the Obstetrics and Gynecology Department of University Hospital La Paz (Madrid, Spain) between January 2017 and June 2023. All twin pregnancies of mother over 45 at the time of delivery as cases ($n = 22$) and 3 controls for each case ($n = 65$) were included. Perinatal outcomes were assessed and compared between singleton pregnancies and twins.
Results: The frequency of preeclampsia was statistically higher in the twin group (27.3% vs 7.7%; $p = 0.017$) (OR 4.5 (1.21–16.65)). Cesarean section was significant more frequent in the twin group (90.9% vs 49.2%; $p = 0.001$) (OR 10.31 (2.23–47.75)). In twins, prematurity rate (68.2% vs 17.2%; $p < 0.001$) and admission to neonatal ICU (63.6% vs 14.5%; $p < 0.001$) were increased. No differences were found in gestational diabetes, pregnancy-induced hypertension, small for gestational age, Apgar test < 7 at 5 min or in the pH < 7.10 in cord blood at birth.
Conclusions: Advanced maternal age is an independent risk factor for adverse perinatal outcomes and obstetric complications, independently of the number of fetuses, especially at extreme fertile ages above 45 years. In the case of twin gestations, risks inherent to twins also increase, such as prematurity, admission to the NICU and CS.

☆ This is a retrospective study, with data from the hospital's electronic records. The study has approval from the hospital for anonymous treatment of patients.

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PALABRAS CLAVE
Edad materna;
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Gemelos;
Embarazo múltiple

Resultados perinatales en gestantes mayores de 45 años: ¿embarazo único o múltiple?

Resumen
Introducción: La edad materna avanzada se asocia con un mayor número de complicaciones obstétricas y resultados perinatales adversos. Cada vez es más común encontrar mujeres embarazadas mayores de 45 años e incluso mayores de 50. Existen pocos estudios que evalúen los resultados perinatales en edades extremas, mayores de 45 años. Por tanto, el objetivo de este estudio es explorar los resultados perinatales en los embarazos de mujeres mayores de 45 años, así como comparar los embarazos gemelares y únicos en esta población.
Material y métodos: Se realizó un estudio observacional retrospectivo de casos y controles en el Servicio de Obstetricia y Ginecología del Hospital Universitario La Paz (Madrid, España) entre enero de 2017 y junio de 2023. Se consideraron casos todos los embarazos gemelares de madre mayor de 45 años en el momento del parto. (n = 22) y 3 controles para cada caso (n = 65). Se evaluaron y compararon los resultados perinatales entre embarazos únicos y gemelares.
Resultados: La frecuencia de preeclampsia fue estadísticamente mayor en el grupo de gemelos (27,3% vs 7,7%, p = 0,017) (OR 4,5 (1,21-16,65)). La cesárea fue significativamente más frecuente en el grupo de gemelos (90,9%, vs 49,2%; p = 0,001) (OR 10,31 (2,23-47,75)). En gemelos, la tasa de prematuridad (68,2% vs 17,2% p< 0,001) y de ingreso a UCI neonatal (63,6% vs 14,5% p< 0,001) fueron mayores. No se encontraron diferencias en diabetes gestacional, hipertensión inducida por el embarazo, tamaño pequeño para la edad gestacional, test de Apgar < 7 a los 5 minutos ni en el pH < 7,10 en sangre de cordón al nacer.
Conclusiones: La edad materna avanzada es un factor de riesgo independiente de resultados perinatales adversos y complicaciones obstétricas, independientemente del número de fetos, especialmente en edades fértiles extremas superiores a los 45 años. En el caso de las gestaciones gemelares también aumentan los riesgos inherentes a los gemelos, como la prematuridad, el ingreso a la UCIN y la cesárea.

Introduction

The age of patients who achieve pregnancy in our environment is increasing. Social changes, the development of a professional career and different family models make women decide, in many cases, to delay the motherhood.

Advanced maternal age is associated with a greater number of obstetric complications and adverse perinatal outcomes such as gestational diabetes, preeclampsia, prematurity, cesarean section (CS) or puerperal complications,[1] both in single and twin pregnancies.[2] Furthermore, the increase in maternal age goes hand in hand with the increase in assisted reproduction techniques (ART) and the probability of achieving a twin pregnancy. In addition, pregnancies get by ART are associated with adverse perinatal outcomes such as preterm birth, small for gestational age, admission to the neonatal intensive unit care (NIUC) meconium aspiration or intraventricular hemorrhage among others,[3] as well as alterations in placental insertion and the umbilical cord.[4]

Until relatively recent years, advanced maternal age was considered in women over 35 years old.[5] This cut-off point has been adapted to the profile of pregnant women today, and advanced maternal age is now considered over 40.[6] Most of the last published works that compare perinatal results according to age groups only take into account the group of people over 40 years of age.[7,8] But, it is increasingly common to find pregnant women over 45 years of age and even over 50. There are few studies that evaluate perinatal outcomes at extreme ages, over 45 years of age.

The vast majority of these pregnant women comes from an ART, so the likelihood of twin pregnancy is increased compared to other age groups, either by the transfer of more than one embryo or by the division of the transferred blast in the case of monochorionic pregnancies, also increased in patients with ART.[9] Fortunately, in recent years, strategies to reduce the rate of twins due to the transfer of two embryos have intensified, with the recommendation of transferring a single embryo. Besides, although the exact causes are unknown, it seems that ART increases the rate of spontaneous division of the transferred blast, thus increasing the rate of monochorionic twin gestation.

On the other hand, twin pregnancies are associated with a higher risk of gestational diabetes and hypertension, and their newborns are associated with a greater risk of prematurity, intrauterine growth restriction, and neonatal death.[10,11] Furthermore, in the case of monochorionic pregnancies, the risks are even greater due to the vascular anastomoses that occur between the fetuses, such as feto-fetal transfusion syndrome, selective intrauterine growth restriction or the anemia–polycythemia sequence.[12]

Because we are witnessing of a progressive increase in twin pregnancies in women over 45 years of age, the objective of this study is to explore perinatal outcomes in the pregnancies of women over 45, as well as to compare twin and singleton pregnancies in this population.

Material and methods

An observational retrospective case–control study was carried out in a tertiary hospital, in the Obstetrics and Gynecology Department of University Hospital La Paz (Madrid, Spain) between January 2017 and June 2023.

A total of 719 pregnant women older than 45 years delivered in our hospital in that period of time. All twin pregnancies of mother over 45 at the time of delivery were included as cases ($n = 22$). The selection of controls was carried out consecutively by date of admission and matched by maternal age at the time of delivery, including 3 controls for each case ($n = 65$).

This study was performed in accordance with the Declaration of Helsinki regarding studies in human subjects.

Medical records were reviewed to collect the following data:

Demographic and reproduction variables: maternal age, date of birth, body mass index (BMI) (kg/m^2), race (caucasian or non causcasian), parity (nuliparity or multiparity), smoking habits (yes/no during pregnancy) or chronic pathology prior to pregnancy (any medical condition as cancer, hypertension, diabetes), type of conception (spontaneous/ART) and type of ART (in vitro fertilization (IVF) and oocyte donation). Likewise, perinatal variables were collected such as pregnancy-induced hypertension (defined as systolic blood pressure higher than 140 mmHg and/or diastolic blood pressure higher than 90 mmHg after 20 weeks of gestational age), preeclampsia (Hypertension with other condition as proteinuria, elevated liver enzymes or thrombopenia), gestational diabetes (diagnosed by positive 100 g oral glucose tolerance test), threat of preterm birth (uterine contractions and short cervix below week 35), preterm labor (labor before 37 weeks of gestation), small for gestational age (estimated fetal weight below the 10th percentile), gestational age at delivery, induction of labor, CS, weight of the newborn, Apgar test, arterial pH in umbilical cord or admission to the neonatal ICU.

The data were collected from the electronic medical record available in our hospital. Variable distribution was tested by the Kolmogorov–Smirnov test. Quantitative variables were expressed as mean standard deviation (SD) or median ($Q1$; $Q3$) as appropriate, and qualitative variables were expressed as relative frequencies (%) and sample size (n). Comparisons between groups were performed by Student's t-test or Mann–Whitney's U-test according to variable distribution. Proportion association was tested by Fisher's exact test. The level of significance was set at 0.05. Statistical analysis was performed with IBM SPSS statistics 20.

Results

Our patients over 45 years old had a dichorionic diamniotic pregnancy in the 72.7% of the cases ($n = 16$), a monochorionic diamniotic pregnancy in the 22.7% ($n = 5$) and only one pregnancy was monochorionic monoamniotic.

When we compared twin pregnancies and singleton pregnancies we did not find differences in median maternal age, median BMI, smoking rate, chronic pathology, race, or ART (Table 1). The method of conception was only obtained from 70 of the patients in the sample, of which 84.3% ($n = 59$) achieved pregnancy through IVF, 41 (80.4%) in singleton pregnancies vs 18 (94.7%) in twins ($p = 0.143$). Of all the patients who achieved pregnancy through IVF, 100% of the single pregnancies were through oocyte donation, while in the case of twin pregnancies, oocyte donation was used in 88.9% of the cases. According with the parity, no significant differences were found, only the 9.1% of twin pregnant women were multiparous comparing with the 28.1% of the singleton group ($p = 0.068$).

Regarding the most common obstetric complications, no differences were found in the rate of gestational diabetes, threat of preterm birth, small for gestational age, abruptio placentae or gestational hypertension (Table 1). However, the frequency of preeclampsia was statistically higher in the twin group comparing with the singleton group (27.3% vs 7.7%, $p = 0.017$), with the risk of developing preeclampsia being 4.5 times greater in twin pregnancies (OR 4.5 (1.21–16.65)) (Table 2)

Of the total number of patients in whom a vaginal birth was attempted ($n = 54$), 63% of them initiated it through induction of labor. Regarding single pregnancies, 68.1% (32/47) had an induction of labor while in the case of twin pregnancies this percentage was only of 28.6% (2/7).

According to the way of delivery, CS was significant more frequent in the twin group (90.9%, vs 49.2%; $p = 0.001$), with an OR of 10.31 (2.23–47.75) (Table 2). In the case of singleton pregnancies, 20 scheduled CS were performed: 10 for previous uterine surgery (previous CS or myomectomy), 5 for breech presentation, one for severe preeclampsia, one for total occlusive placenta previa, and 3 elective CS. The rest of the CS were intrapartum, 11 of them due to labor dystocia (pelvic–cephalic disproportion, non-progression of labor or failure of induction) and one of them due to risk of loss of fetal well-being.

Regarding CS in twin pregnancies, the majority were elective due to maternal age or twin pregnancy ($n = 10$), 4 scheduled CS due to previous uterine surgery, one c-section due to maternal pathology and 2 due to transverse situation of the first twin. Only 3 CS were performed intrapartum, 2 due to non-progression of labor and 1 due to risk of loss of fetal well-being.

Significant differences were found in gestational age at delivery (34.73 w vs 38.28 w $p < 0001$), prematurity rate (delivery < 37 weeks) (68.2% vs 17.2%, $p < 0.001$), weight of the newborn at delivery (2141 vs 3095, $p < 0.001$), and admission to neonatal ICU (63.6% vs 14.5%, $p < 0.001$) (Fig. 1). Nevertheless, no differences were found in the Apgar test < 7 at 5 min or in the pH < 7.10 in cord blood at birth. The risk of preterm birth and admission to neonatal ICU were 10 times higher in twin pregnancies (OR 10.325 (3.41–31.25) and OR 10.306 (3.36–31.58) respectively) (Table 2).

Other unfrequent maternal complications were recorded in our patients: 2 cases of puerperal hemorrhages, three pregnant women with intrahepatic cholestasis of pregnancy and two patients with placental accreta, without finding a relationship with twins.

Only one antepartum fetal death was recorded in one of the twins at week 21. Additionally, in the group of singleton pregnancies, one fetus was diagnosed with ventricular septal defect, another with cleft palate, and another fetus with tricuspid insufficiency. Regarding fetal complications in the twin group, a fetal transfusion syndrome was diagnosed that

Table 1 Perinatal characteristics and outcomes in single and multiple pregnancies in pregnant women over 45 years of age.

Characteristics and results	Singleton pregnancies $N = 65$	Twin pregnancies $N = 22$	p
Maternal age (IR)	46 (3)	45.5 (8)	*0.176*
Maternal BMI kg/m^2 (IR)	23.5 (5.08)	28.38 (8.32)	*0.1*
Smokers (%)	4 (6.2)	1 (5)	*0.848*
Caucasians (%)	56 (88.9)	21 (95.5)	*0.632*
Nuliparous (%)	46 (71.9)	20 (90.9)	*0.068*
IVF (%)	41 (63.1)	18 (81.8)	*0.143*
Egg donors (% among IVF)	40 (97.6)	16 (88.9)	*0.605*
Gestational diabetes (%)	12 (18.4)	5 (22.7)	*0.885*
Abruptio placentae (%)	1 (1.5)	0	*0.558*
Preeclampsia (%)	5 (7.7)	6 (27.3)	*0.017*
Gestational hypertension (%)	4 (6.2)	1 (4.5)	*0.779*
Threat of premature birth (%)	3 (4.6)	3 (13.6)	*0.149*
Small for gestational age (%)	7 (10.8)	3 (14.3)	*0.662*
Gestational age at birth (IR)	39 (2)	35 (11)	*<0.001*
Preterm birth (%)	11 (17.2)	15 (68.2)	*<0.001*
Induction (%)	32 (68.1)	2 (28.6)	*0.043*
Instrumental delivery (%)	9 (13.8)	0	*0.334*
Eutocic delivery (%)	24 (36.9)	2 (9.1)	*0.014*
Cesarean section (%)	32 (49.2)	20 (90.9)	*0.001*
Apgar ≤ 7 at 5 min (%)	3 (4.8)	2 (9.5)	*0.424*
pH < 7.10 (%)	4 (6.3)	2 (9.1)	*0.666*
Birthweight (SD)	3095 (570)	2141 (485.9)	*<0.001*
Birthweight 2 twin (IR)	–	1198 (770)	–
Neonatal ICU admission (%)	9 (14.5)	14 (63.6)	*<0.001*

SD: standard deviation; IR: interquartile range.

Table 2 Odds ratio. Twins vs singleton pregnancies.

	OR	95% confidence intervals
Preeclampsia	4.5	1.21–16.65
Preterm birth	10.325	3.411–31.251
Cesarean section	10.313	2.23–47.75
Neonatal ICU admission	10.306	3.36–31.58

was treated with intrauterine laser at week 25, one fetus with Tetralogy of Fallot and another with a laterocervical solid cystic mass and multicystic kidney.

Discussion

Pregnancies in the age group over 45 years are rare, although it is increasingly common to find them in high-risk units, especially in large national reference hospitals. In our center, with more than 5000 deliveries per year, 110 patients are over 45 years old, which represents approximately 2% of the delivers each year. Therefore, it is not easy to obtain conclusions about the specific risks of these patients. These data only include patients who had a delivery of more than 24 weeks, not including all patients who had a first trimester pregnancy loss. Given that the abortion rate is higher than in the general population, the number of women of this age who achieved pregnancy is probably much higher.[13]

Most of these women achieve their pregnancies through ART and more than 90% are with egg donation, which already entails risks associated with these techniques. Furthermore, advanced maternal age makes the pregnant profile more pathological; patients are more likely to have an underlying disease, whether cardiovascular, metabolic or autoimmune. Most of them have years of sterility or infertility, numerous diagnostic tests and treatments performed that have delayed their motherhood.

In the case of gestational diabetes, the prevalence in Spain is 12%,[16] while in our patients over 45 years of age was 19.5% with no differences found between singletons and twins, Therefore, it is a factor independent of the number of fetuses and the type of gestation. It is known that age is a very important risk factor for the development of gestational diabetes, so the rate found in our patients is consistent.[14]

On the other hand, the rate of preeclampsia in our sample is higher in twin pregnancies than in singleton pregnancies. This has been observed in numerous studies regardless of

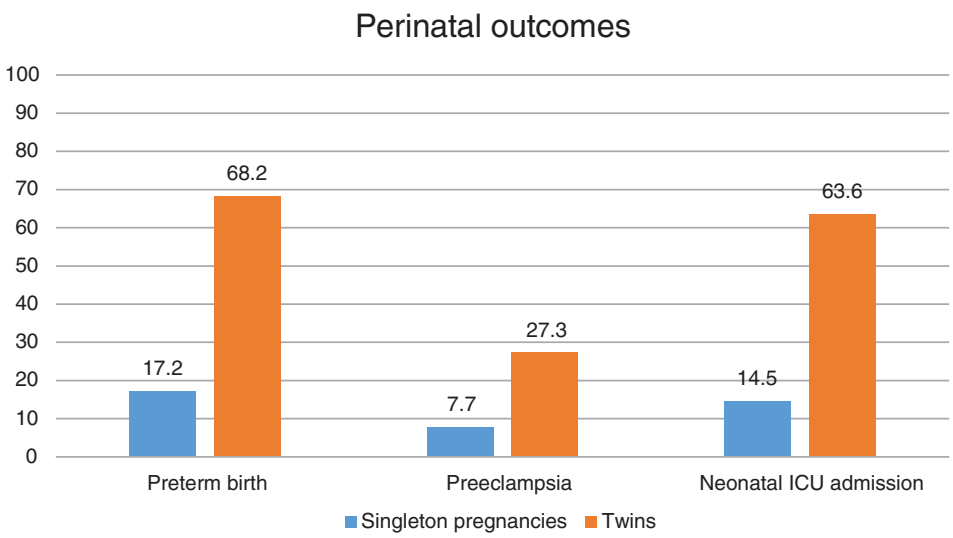

Figure 1 Perinatal outcomes (%).

age. The cause of the increased risk of preeclampsia in twins is unknown and there are numerous theories, such as the fact that the placenta is larger, there is worse perfusion or a greater imbalance of angiogenic factors in these pregnancies.[15,16] The rate of preeclampsia in the singleton group is similar that the pregnant population and it can be explained because of the administration of aspirin 150 to every single pregnant woman with a higher risk of preeclampsia in the first trimester screening since 2017.

Comparing with the general population of twin pregnancies, the prematurity rate is similar. It can be explained because in our protocol of preventing prematurity in all twin pregnancies, we measure the uterine cervix from 20th to 34th weeks of gestation and place a cervical pessary when the cervix is shorter than 25 mm. In our study dichorionic diamniotic pregnancies had a prematurity rate of 62.5% and 80% in monochorionic diamniotic pregnancies, whereas that in general population is 48.6% and 88.6% respectively.[17] In singleton pregnancies over 45 years of age, we observed a prematurity rate of 17%, while the mundial average is around 10% of all live newborns. Although this figure is slightly higher, it is still an acceptable rate if we compare it with twin pregnancies in which prematurity increases in any range of maternal age.[18] We can explain the higher rate of prematurity in these population of pregnant women over 45 because of the increase of preeclampsia that leads to an increase in early pregnancy terminations.

The CS rate in our study group was 59.8% (49.2% in singleton pregnancies vs 90.9% in twin pregnancies). It should be noted that the rate of CS in the case of twins is increased by the fact of the twin gestation itself and not only by age, since the position of the first twin and the chorionicity (monochorionic–monoamniotic) often lead us it will lead to a scheduled CS, a fact that will never occur in a single pregnancy. Furthermore, with age, the uterine cervix is closer and less elastic ant the uterine contractions are less effective increasing the rate of inductions of labor and cesarean section for failure of the induction

Rademaker et al. evaluates the perinatal outcomes of singleton pregnancies over 45 and concluded that in singleton pregnant women above 45 there is a risk of up to three times greater perinatal death and gestational diabetes and a risk of six times of CS, with respect to a control group of patients between 25 and 29 years old. Also in the group of pregnant women over 50 years of age had a seven times higher risk of CS, a four times higher risk of gestational diabetes, postpartum hemorrhage, and neonatal intensive care unit admission, and a 10 times higher risk of hypertensive disorders.[19] We found as well an increase number of CS and gestational diabetes comparing with the average in pregnant population, but we did not find and increase of fetal demise. In our sample, only the intrauterine death of one of the twins at week 2 was reported, and no perinatal death was found.

Laskov et al. compare twin pregnancies in patients over 45 versus under 40 years of age and conclude that in the first group there is a greater risk of preterm birth, as well as more maternal complications such as admission to the NICU and a greater need for maternal transfusion of blood components.[20] Consistent with these findings, our study also observed a higher rate of prematurity in general but especially in twin pregnancies. Perinatal outcomes were worse in the twin pregnancies, mainly due to the associated prematurity.

Regarding the studies published so far on twin pregnancies in patients with advanced maternal age, the results are disparate. Several authors have published on the subject in recent years, however some of them consider patients over 35 as advanced age so it would not be comparable with our population. In this way, a very recent meta-analysis that includes 13 studies compares twin pregnancies in patients more or less 35 years old and concludes that the results are similar in both groups, only finding a higher rate of gestational diabetes and CS in patients over 35 years old.[21] Another meta-analysis published in 2023 found a higher rate of diabetes, hypertension and prematurity in twin pregnancies over 40 years of age compared to younger

pregnant women, which agrees with our data except the hypertension.[22]

We are facing a group of patients with a different baseline profile only due to age, a higher rate of chronic pathology that leads to higher hypertension, gestational diabetes and maternal complications.

When comparing single and twin pregnancies in this group, there are some differences, especially those associated with twin pregnancies in general, such as premature birth or preeclampsia. However, there are no differences in gestational diabetes or small fetuses for gestational age.

As limitations of our study, we can highlight that the sample size is low, only 22 twin pregnancies analyzed. However, the pregnancy rate in this age group is truly low, so this sample size in a single center could be considered one of the strengths of the study. Furthermore, no previous studies have been found in the literature that compare single and multiple gestations in women over 45 years of age, a group of pregnant women which is increasing in Western Countries. All studies on advanced maternal age set the cut-off point at 35 years, a concept that must change according to changes we currently live in.

Conclusions

Advanced maternal age is an independent risk factor for adverse perinatal outcomes and obstetric complications, independently of the number of fetuses, especially at extreme fertile ages above 45 years. Twin pregnancies in this age group are not frequent, so analyzing the associated risks is complicated. Most of the pregnancies in women over 45 comes from an egg-donor IVF.

In the case of twin gestations, risks inherent to twins are also increase, such as prematurity, admission to the NICU and CS. Comparing with singleton pregnancies, twin pregnancies in patients over 45 do not have an increased risk of gestational diabetes, abruptio placentae, threat of premature birth, small for gestational age, low score on the Apgar test or acidosis in cord blood.

These results are a great source of information and can help when advising and counseling future parents and professionals about maternal and fetal complications in ART before transferring 2 embryos.

Ethical disclosures

Protection of human and animal subjects. The authors declare that no experiments were performed on humans or animals for this research.

Confidentiality of data. The authors declare that they have followed their workplace protocols on the publication of patient data.

Right to privacy and informed consent. The authors declare that no patient data appear in this article.

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Conflicts of interest

The authors report no conflicts of interest.

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References

1. Landry M, Allouche M, Vayssière C, Guerby P, Grousolles M. Maternal and perinatal outcomes in women aged 42 years or older. Int J Gynaecol Obstet. 2023, http://dx.doi.org/10.1002/ijgo.15160. Epub ahead of print. PMID: 37776016.
2. Whittaker M, Greatholder I, Kilby MD, Heazell AEP. Risk factors for adverse outcomes in twin pregnancies: a narrative review. J Matern Fetal Neonatal Med. 2023;36:2240467, http://dx.doi.org/10.1080/14767058.2023.2240467. PMID: 37518183.
3. Singh N, Malhotra N, Mahey R, Patel G, Saini M. In vitro fertilization as an independent risk factor for perinatal complications: single-center 10 years cohort study. JBRA Assist Reprod. 2023;27:197–203, http://dx.doi.org/10.5935/1518-0557.20220041. PMID: 37014951; PMCID: PMC10279444.
4. Fukuda E, Hamuro A, Kitada K, Kurihara Y, Tahara M, Misugi T, et al. The impact of assisted reproductive technology on umbilical cord insertion: increased risk of velamentous cord insertion in singleton pregnancies conceived through ICSI. Medicina (Kaunas). 2023;59:1715, http://dx.doi.org/10.3390/medicina59101715. PMID: 37893433; PMCID: PMC10608747.
5. Kirz DS, Dorchester W, Freeman RK. Advanced maternal age: the mature gravida. Am J Obstet Gynecol. 1985;152:7–12, http://dx.doi.org/10.1016/s0002-9378(85)80166-6. PMID: 3993714.
6. Tambvekar SE, Adki S, Sheriar NK. Pregnancies in elderly mothers over 40 years: what to expect from the rising new age high-risk cohort? J Obstet Gynaecol India. 2023;73:358–62, http://dx.doi.org/10.1007/s13224-022-01701-3. Epub 2023 Mar 27: PMID: 37701086; PMCID: PMC10492723.
7. Guarga Montori M, Álvarez Martínez A, Luna Álvarez C, Abadía Cuchí N, Mateo Alcalá P, Ruiz-Martínez S. Advanced maternal age and adverse pregnancy outcomes: a cohort study. Taiwan J Obstet Gynecol. 2021;60:119–24, http://dx.doi.org/10.1016/j.tjog.2020.11.018. PMID: 33494983.
8. De la Calle M, Bartha JL, García L, Cuerva MJ, Ramiro-Cortijo D. Women aged over 40 with twin pregnancies have a higher risk of adverse obstetrical outcomes. Int J Environ Res Public Health. 2021;18:13117, http://dx.doi.org/10.3390/ijerph182413117. PMID: 34948726; PMCID: PMC8701912.
9. Dallagiovanna C, Vanni VS, Somigliana E, Busnelli A, Papaleo E, Villanacci R, et al. Risk factors for monozygotic twins in IVF-ICSI cycles: a case–control study. Reprod Sci. 2021;28:1421–7, http://dx.doi.org/10.1007/s43032-020-00406-0. Epub 2020 Nov 30: PMID: 33258063.
10. Meyer R, Orvieto R, Israel A, Mohr-Sasson A, Timerman Y, Gorodesky T, et al. Outcomes of singleton versus twin pregnancies in the fifth and sixth decades. Eur J Obstet Gynecol Reprod Biol. 2018;231:255–61, http://dx.doi.org/10.1016/J.EJOGRB.201811007.

11. Embarazo gemelar bicorial. Guia de asistencia práctica de la Sociedad Española de Ginecologia y obstetricia (SEGO). 2015.
12. Gestación monocorial. Guia de asistencia práctica de la Sociedad Española de Ginecologia y obstetricia (SEGO). 2019.
13. Leader J, Bajwa A, Lanes A, Hua X, Rennicks White R, Rybak N, et al. The effect of very advanced maternal age on maternal and neonatal outcomes: a systematic review. J Obstet Gynaecol Can. 2018;40:1208–18, http://dx.doi.org/10.1016/j.jogc.2017.10.027. Epub 2018 Apr 19: PMID: 29681506.
14. Diabetes mellitus y embarazo. Guía de práctica clínica actualizada 2021. Sociedad Española de Ginecología y Obstetricia (SEGO), Grupo Español de Diabetes y Embarazo (GEDE). Prog Obst Ginecol. 2022;65:35–41.
15. Aviram A, Giltvedt MK, Sherman C, Kingdom J, Zaltz A, Barrett J, et al. The role of placental malperfusion in the pathogenesis of preeclampsia in dichorionic twin and singleton pregnancies. Placenta. 2018;70:41–9, http://dx.doi.org/10.1016/j.placenta.2018.09.002. Epub 2018 Sep 7: PMID: 30316326.
16. Bdolah Y, Lam C, Rajakumar A, Shivalingappa V, MutterW, Sachs BP, et al. Twin pregnancy and the risk of preeclampsia: bigger placenta or relative ischemia? Am J Obstet Gynecol. 2008;198:428, http://dx.doi.org/10.1016/J.AJOG.200710783, e1–e6.
17. Martin JA, Hamilton BE, Osterman MJK, Driscoll AK. Births: final data for 2019. Natl Vital Stat Rep. 2021;70:1–51. PMID: 33814033.
18. Blencowe H, Cousens S, Oestergaard MZ, Chou D, Moller AB, Narwal R, et al. National, regional, and worldwide estimates of preterm birth rates in the year 2010 with time trends since 1990 for selected countries: a systematic analysis and implications. Lancet. 2012;379:2162–72, http://dx.doi.org/10.1016/S0140-6736(12)60820-4. PMID: 22682464.
19. Rademaker D, Hukkelhoven CWPM, van Pampus MG. Adverse maternal and perinatal pregnancy outcomes related to very advanced maternal age in primigravida and multigravida in the Netherlands: a population-based cohort. Acta Obstet Gynecol Scand. 2021;100:941–8, http://dx.doi.org/10.1111/aogs.14064. Epub 2021 Feb 27: PMID: 33314021.
20. Laskov I, Michaan N, Cohen A, Tsafrir Z, Maslovitz S, Kupferminc M, et al. Outcome of twin pregnancy in women ≥45 years old: a retrospective cohort study. J Matern Fetal Neonatal Med. 2013;26:669–72, http://dx.doi.org/10.3109/14767058.2012.746298. Epub 2012 Dec 14: PMID: 23241057.
21. Zipori Y, Linder R, Khatib N, Weiner Z, Barzilay E. Advanced maternal age and perinatal outcome in twin pregnancies: a meta-analysis. J Matern Fetal Neonatal Med. 2020;33:3193–9, http://dx.doi.org/10.1080/14767058.2019.1570112. Epub 2019 Jan 29: PMID: 30696313.
22. Xiong QF, Yu ZH, Zhang AL, Zhu XH. Impact of maternal age on perinatal outcomes in twin pregnancies: a systematic review and meta-analysis. Eur Rev Med Pharmacol Sci. 2022;26:99–109, http://dx.doi.org/10.26355/eurrev_202201_27753. PMID: 35049025.