Placenta 150 (2024) 1–7

Contents lists available at ScienceDirect

Placenta

journal homepage: www.elsevier.com/locate/placenta

Paternal age and first trimester placental size and growth: The Rotterdam Periconceptional Cohort

M.M. Van Vliet [a,b], S. Schoenmakers [a], B. Haug [a], S. Willemsen [c], R.P.M. Steegers-Theunissen [a,*]

[a] Department of Obstetrics and Gynaecology, Erasmus MC, University Medical Center, Rotterdam, the Netherlands
[b] Department of Developmental Biology, Erasmus MC, University Medical Center, Rotterdam, the Netherlands
[c] Department Biostatistics, Erasmus MC, University Medical Center, Rotterdam, the Netherlands

ARTICLE INFO

Keywords:
Aging
Pregnancy
Semen
Development

ABSTRACT

Introduction: Despite a noticeable trend of delayed fatherhood, less is known about the impact of paternal age on the paternally programmed placenta. We hypothesize that paternal aging affects seminal quality and as such induces ageing-related epigenetic alterations that influence placental growth. Our main aim is to investigate associations between paternal age and first trimester (vascular) placental growth trajectories.
Methods: Pregnant women were enrolled before 10 weeks of gestation in the Rotterdam Periconceptional Cohort (Predict study). Placental volumes (PV) and utero-placental vascular volumes (uPVV) were measured at 7, 9, and 11 weeks gestation. Associations between paternal age and PV and uPVV were investigated using linear mixed models and the maximum likelihood ratio test to test non-linear relationships. We adjusted for gestational age, fetal sex, parental smoking and maternal age, BMI, education and parity, and stratified for conception mode.
Results: From 808 pregnancies we obtained 1313 PV and from 183 pregnancies 345 uPVV measurements. We show no associations between paternal age and PV ($p = 0.934$) and uPVV ($p = 0.489$) in our total population or in pregnancies conceived naturally (PV $p = 0.166$; uPVV $p = 0.446$) and after IVF/ICSI (PV $p = 0.909$; uPVV $p = 0.749$). For example, PV was 0.9% smaller (95% CI -5.7%—7.1%) in fathers aged 40 compared to 30 years old at 9 weeks gestation in the total study population.
Discussion: We are not demonstrating a significant impact of paternal age on first trimester placental growth in a tertiary care population. Given the trend of increasing paternal age, our study should be repeated in the general population.

1. Introduction

Appropriate placental growth and development are essential for a healthy pregnancy and both underweight and overweight placentas are associated with unfavorable pregnancy outcomes [1,2]. While developed countries have witnessed a noticeable trend of delayed parenthood [3], pregnancies of older women tend to have a higher placental weight and placental weight-to-birth weight ratio [4]. On the other hand, advanced maternal age is also associated with increased risks of pregnancy complications, such as miscarriage, hypertensive disorders of pregnancy (HDP) and fetal growth restriction, outcomes that are associated with lower placental weights [5–10]. Although paternal age is also increasing, limited and conflicting data are available on the associations between paternal age and placental growth or pregnancy outcomes. A small increase in placental weight and placental weight-to-birth weight ratio has been reported among older fathers (>50 years old) [11], while a lower placental weight and placental weight-to-birth weight ratio were found in mice with advanced paternal age [12]. Additionally, some studies found no associations between paternal age and low birth weight [13,14] or HDP [14,15], while others reported so-called U-shaped relationships with increased risks for these adverse outcomes in pregnancies with both younger (<25 years) or older (45+ years) fathers [15–20].

Epigenetic modifications are suggested as a potential mechanism between the potential impact of paternal conditions and placental growth and function [21]. Epigenetic mechanisms such as DNA methylation can alter gene expression and play a crucial role in various biological processes, including cell differentiation and genomic

Abbreviations: PV, placental volume; uPVV, utero-placental vascular volume.

* Corresponding author. Department of Obstetrics and Gynecology, Erasmus University Medical Centre, PO Box 2040, 3000 CA, Rotterdam, the Netherlands.
E-mail address: r.steegers@erasmusmc.nl (R.P.M. Steegers-Theunissen).

https://doi.org/10.1016/j.placenta.2024.03.009
Received 1 December 2023; Received in revised form 6 March 2024; Accepted 15 March 2024
Available online 21 March 2024

imprinting [22]. Overall, paternally expressed imprinted genes are particularly expressed in the placenta and largely stimulate placental growth [23,24]. Since age-related DNA methylation differences are observed in sperm cells, aging-induced epigenetic alterations are hypothesized to result in abnormal gene expression and could consequently affect placental growth and pregnancy outcomes [25,26].

Placental growth is typically only studied after delivery by measuring placental weight. However, innovative 3D ultrasound techniques using V-scope software enable the in vivo assessment of utero-placental (vascular) development during pregnancy already in the first trimester of pregnancy [27,28]. We hypothesize that smaller placental (vascular) growth occurs in pregnancies conceived by older fathers, because of potential aging-induced epigenetic alterations leading to dysregulation of paternally expressed genes which generally promote placental growth [23–25]. This would be in line with the previous study conducted in mice which took place in a well-controlled setting [12]. We further hypothesize that paternal age has the largest measurable effect very early in pregnancy because of accumulating effects of (maternal) conditions on placental growth across pregnancy. Therefore, our aim is to investigate associations between paternal age and features of first trimester (vascular) placental growth. A second aim is to investigate associations between paternal age and placental-related complications including HDP and small for gestational age (SGA) offspring.

2. Methods

2.1. Study population

All data were collected in the Rotterdam Periconceptional cohort (Predict study), an ongoing prospective tertiary hospital-based birth cohort conducted at the Department of Obstetrics and Gynecology of the Erasmus MC, University Medical Center, The Netherlands [29,30]. Women of at least 18 years old with a singleton pregnancy before 10 weeks of gestation were eligible for participation. For this study, participants were recruited from November 2010 till December 2020. The VIRTUAL placenta study was embedded as subcohort between January 2017 to March 2018 and had the same eligibility criteria as the Predict study. In our analyses, we excluded pregnancies in case of miscarriage, intrauterine fetal death, known fetal congenital anomalies, twins, gamete donation, pregnancies after the transfer of a cryopreserved embryo >1 year old, unknown paternal age or in case of study withdrawal. Both parents signed a written informed consent form at enrollment.

2.2. Study parameters

Maternal and paternal characteristics were obtained through validated self-reported questionnaires. Weight and height were measured at study entry. Naturally conceived pregnancies in women with a regular cycle between 25 and 31 days were dated based on their first day of their last menstrual period (LMP). For women with irregular cycles or unknown LMP, the dating was based on the crown-rump length (CRL) measured at the 9th week ultrasound. If the gestational age based on LMP differed ≥6 days from the gestational age as calculated by the CRL, dating was based on the CRL. Pregnancies conceived through ovulation induction or intrauterine insemination (IUI) were considered naturally conceived. IUI pregnancies were dated based on insemination date. In vitro fertilization (IVF) and intracytoplasmic sperm injection (ICSI) pregnancies were dated based on conception date [29,30]. For IVF/ICSI pregnancies, paternal age was based on the date of sperm retrieval or ejaculation date where appropriate.

2.3. Ultrasound variables

Placental volume (PV) was measured in both the Predict study and the Virtual Placenta Study, while the utero-placental vascular volume (uPVV) was measured only in this subcohort [29]. Measurement of PV and uPVV have extensively been described previously and have good to excellent intra- and inter-observer agreement [27,28]. In short, PV and uPVV were measured using internal 3D ultrasound volumes of the whole pregnancy with standardized settings, where 3D power Doppler ultrasound was used to specifically visualize the uPVV. All measurements were performed in the 7th, 9th and 11th week of gestation by using a 6–12 MHz transvaginal probe compatible with the GE Voluson E8 Expert system.

Afterwards, PV was measured offline by using Virtual Organ Computer-aided AnaLysis (VOCAL). Using the VOCAL algorithm, twelve segments of the trophoblast were made using a rotational step of 15°. Total pregnancy volume and the volume of the gestational sac were manually measured for all twelve sections. PV was calculated as total pregnancy volume minus the volume of the gestational sac. The uPVV was measured offline using a Virtual Reality (VR) desktop system. This projects the ultrasound datasets as a hologram and allows for accurate removal of embryonic and myometrial blood vessels. The uPVV is the volume of the remaining blood vessels up to the utero-placental border. Quality of the images was scored and volumes rated as insufficient quality due to, for example, movement artefacts, acoustic shadowing or incompleteness were excluded before analysis [27].

2.4. Pregnancy outcome variables

All pregnancy outcomes, i.e., birth weight, fetal sex, date of delivery, pregnancy induced hypertension (PIH) and preeclampsia (PE) were retrieved from medical records. PIH was defined as newly onset systolic blood pressure above 140 mmHg and/or a diastolic blood pressure above 90 mmHg [31]. PE was defined as newly onset hypertension after 20 weeks of gestation and the presence of proteinuria (>300 mg) in 24 h urine [32]. We defined small for gestational age (SGA) as birth weight percentile < p10 according to Hoftiezer birth-weight charts [33].

2.5. Statistical analysis

We stratified the analysis according to mode of conception into pregnancies naturally conceived and after IVF/ICSI treatment, since assisted reproductive technologies have been reported to affect placental weight and parental age is associated with use of fertility treatment [34]. Baseline characteristics between groups were compared using the Mann-Whitney *U* test for continuous variables and the chi-square test for categorical variables.

Linear mixed models were used to assess associations between paternal age and repeated measurements of PV and uPVV. Because of the skewed distributions of PV and uPVV, we used a cubic root transformation to obtain linearity and normality of residuals and random effects. The likelihood ratio test was used to compare between models without paternal age and paternal age plus paternal age^2 to account for potential non-linear or U-shaped relationships. An interaction term containing paternal age and gestational age at the moment of the ultrasound was included since we hypothesized that the effect of paternal age on placental growth trajectories differs over gestation, with the largest effect very early in pregnancy because of accumulating effects of other (maternal) conditions and exposures on placental growth over gestation.

In model 1 we adjusted for gestational age at the moment of the ultrasound and model 2 was additionally adjusted for parity, fetal sex, periconceptional parental smoking, and maternal age, BMI, and education based on previous literature and insight of correlations between the covariates. Since first trimester placental growth is associated with adverse pregnancy outcomes, a sensitivity analysis was performed excluding pregnancies complicated by PE, PIH and SGA [9,10,28].

The associations between paternal age and HDP and SGA were assessed using logistic regression analyses. We made a crude model (model 1) and a multivariable model adjusted for above mentioned

covariates and mode of conception (model 2). When investigating SGA, we did not adjust for fetal sex since Hoftiezer birth-weight charts are sex-specific. P-values ≤0.05 were considered statistically significant and all analyses were performed using SPSS package 28.0 (IBM SPSS Statistics, Armonk, NY) and R (Version 4.2.1).

3. Results

3.1. Baseline

We included 2051 first trimester pregnancies in the Predict study between November 2010 and December 2020. We excluded 526 pregnancies prior to analysis because of miscarriage or termination of pregnancy (TOP) (n = 175), unknown paternal age (n = 95), pregnancy after the transfer of a cryopreserved embryo >1 year old (n = 35), twin pregnancies (n = 66), fetal congenital malformations (n = 54), gamete donation (n = 46), study withdrawal (drop-outs) (n = 39) and intra-uterine fetal deaths (IUFD) (n = 16). Of the 1525 remaining pregnancies, 825 had at least one PV or uPVV measurement available with a total of 1313 PV and 345 uPVV measurements. For our secondary outcomes, medical reports were available for 1449 of 1525 included pregnancies (Fig. 1).

Baseline characteristics of couples with available ultrasound data and available medical reports are depicted in Table 1 and S1, respectively. Of couples with available ultrasounds, 475 pregnancies were naturally conceived and 350 after IVF/ICSI. Compared to naturally conceived pregnancies, the median age at conception was slightly higher for pregnancies conceived after IVF/ICSI for both men (34.9 vs 33.3 years, $p < 0.001$) and women (33.0 vs 31.2 years, $p < 0.001$), fathers had a slightly higher BMI (26.7 kg/m^2 vs 25.7 kg/m^2, $p = 0.003$) and women were more often nulliparous (73.4% vs 45.3%, $p < 0.001$), started with folic acid supplements more often before conception (94.0% vs 72.0%, $p < 0.001$) and were less likely to consume alcohol in the periconceptional period (22.0% vs 37.3%, $p < 0.001$).

3.2. Associations between paternal age and PV and uPVV

In the total study population, we found no significant associations between paternal age and PV in model 1 ($p = 0.742$) and model 2 ($p = 0.934$). After stratification for mode of conception, we also found no significant association for naturally conceived pregnancies (model 1 $p = 0.179$; model 2 $p = 0.166$) and for pregnancies conceived after IVF/ICSI (model 1 $p = 0.101$; model 2 $p = 0.909$). To visualize the relationship between paternal age and PV, effect plots are shown for model 2 for the total study population and stratified for mode of conception at a gestational age of 7 weeks, 9 weeks and 11 weeks (Fig. 2A–C). In the total study population and in IVF/ICSI pregnancies, no significant associations are observed between paternal age and PV (Fig. 2A and C). In naturally conceived pregnancies, a non-significant ($p = 0.166$) association is observed with a tendency to larger PVs in both younger and older fathers (Fig. 2B). The number of fathers with more extreme ages, especially <25 years or >45 years old, is limited in all study groups (Fig. 2A–C). To illustrate the magnitude of effects, the back-transformed PV of for example 40 years old fathers compared to 30 years old fathers is 0.9% smaller (95% CI -5.7%—7.1%) at a gestational age of 9 weeks in the total study population. The effect plots for model 1 are shown in Fig. S1.

In the subpopulation with available uPVV measurements, no significant association was found between paternal age and uPVV in the total study population for both models (model 1: $p = 0.809$; model 2: $p = 0.489$) or stratified for naturally conceived pregnancies (model 1: $p = 0.722$; model 2: $p = 0.446$) and IVF/ICSI pregnancies (model 1: $p = 0.887$; model 2: $p = 0.749$). Comparable results were found in the sensitivity analyses for the relation between paternal age and PV or uPVV after excluding pregnancies complicated by HDP or pregnancies with SGA offspring (data not shown).

3.3. Secondary outcomes

Table 2 shows the pregnancy outcomes in the study population

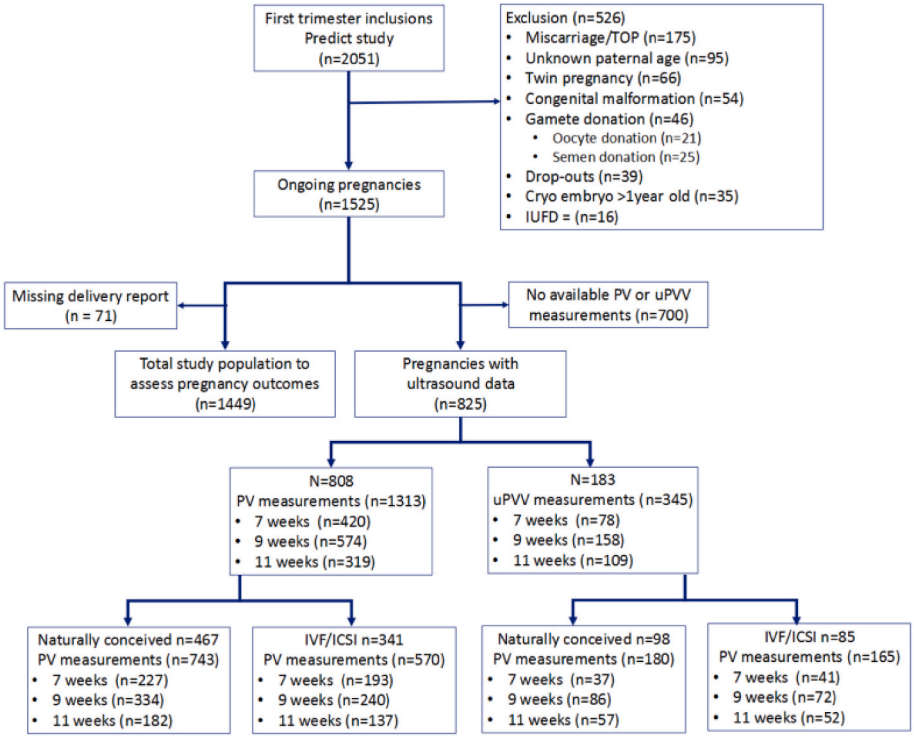

Fig. 1. Flowchart of total study population. TOP = termination of pregnancy, IUFD = intra-uterine fetal death, PV = placental volume, uPVV = utero-placental vascular volume.

Table 1
Baseline characteristics of included couples with available ultrasound data stratified for mode of conception.

	Total study population	Naturally conceived pregnancies	IVF/ICSI pregnancies	P-value
Men	n = 825	n = 475	n = 350	
Age (years)	33.9 [30.9–38.3]	33.3 [30.2–37.6]	34.9 [31.4–39.0]	**<0.001***
Geographic origin				0.317
Dutch	613 (74.3)	357 (75.2)	256 (73.1)	
Western	24 (2.9)	17 (3.6)	7 (2.0)	
Non-Western	88 (10.7)	56 (11.8)	32 (9.1)	
Missing	*100 (12.1)*	*45 (9.5)*	*55 (15.7)*	
Educational level				0.304
Low	95 (11.5)	55 (11.6)	40 (11.4)	
Intermediate	282 (34.2)	159 (33.5)	123 (35.1)	
High	340 (41.2)	212 (44.6)	128 (36.6)	
Missing	*108 (13.1)*	*49 (10.3)*	*59 (16.9)*	
BMI at study entry (kg/m^2)	26.0 [23.7–28.6]	25.7 [23.5–28.1]	26.7 [24.0–29.3]	**0.003***
Missing	*106*	*56*	*50*	
Periconceptional alcohol use	534 (64.7)	320 (67.4)	214 (61.1)	0.609
Missing	*99 (12.0)*	*44 (9.3)*	*55 (15.7)*	
Periconceptional smoking	222 (26.9)	139 (29.2)	83 (23.7)	0.237
Missing	*99 (12.0)*	*44 (9.3)*	*55 (15.7)*	
Women	n = 825	n = 475	n = 350	
Age (years)	32.1 [29.0–35.4]	31.2 [28.7–34.7]	33.0 [29.8–36.1]	**<0.001***
Nulliparous	472 (57.2)	215 (45.3)	257 (73.4)	**<0.001***
Missing	*6 (0.7)*	*6 (1.3)*	–	
Geographic origin				0.716
Dutch	653 (79.2)	383 (80.6)	270 (77.1)	
Western	44 (5.3)	24 (5.1)	20 (5.7)	
Non-Western	98 (11.9)	54 (11.4)	44 (12.6)	
Missing	*30 (3.6)*	*14 (2.9)*	*16 (4.6)*	
Educational level				0.663
Low	54 (6.5)	33 (6.9)	21 (6.0)	
Intermediate	273 (33.1)	153 (32.2)	120 (34.3)	
High	468 (56.7)	276 (58.0)	192 (54.9)	
Missing	*30 (3.6)*	*13 (2.7)*	*17 (4.9)*	
BMI at study entry (kg/m^2)	24.5 [22.1–28.2]	24.6 [22.2–28.5]	24.3 [22.0–28.0]	0.235
Missing	*13*	8	*5*	
Folic acid supplement use	809 (98.1)	465 (97.9)	344 (98.3)	NA
Missing	*16 (1.9)*	*10 (2.1)*	*6 (1.7)*	
Started preconceptionally	671 (81.3)	342 (72.0)	329 (94.0)	**<0.001***
Missing	*39 (4.7)*	*23 (4.8)*	*16 (4.6)*	
Periconceptional alcohol use	254 (30.8)	177 (37.3)	77 (22.0)	**<0.001***
Missing	*20 (2.4)*	*12 (2.5)*	*8 (2.3)*	
Periconceptional smoking	116 (14.0)	68 (14.3)	48 (13.7)	0.795
Missing	*20 (2.4)*	*12 (2.5)*	*8 (2.3)*	

Data are presented as median [interquartile range (IQR)] or n (%). *Significance at $p \leq 0.05$ assessed by chi-square test or Mann Whitney *U* test as appropriate.

stratified by paternal age categories. The number of fathers aged <25 years or >45 years old was again limited (Table 2). Hypertensive disorders complicated 9.6% of pregnancies (n = 139). The median gestational age at birth was 39 weeks and 1 day [IQR 38+0–40 + 1] and the median birth weight was 3340 g [IQR 2965gr–3680gr]. Based on Hoftiezer birth weight percentiles, 12.6% of newborns (n = 182) were born SGA and 5.3% (n = 77) had a birth weight < p3.

Due to a lack of power, we pooled PIH and PE in the analyses and did not stratify for mode of conception, but included mode of conception as covariate in the adjusted model. Paternal age >50 years of age was significantly association with less HDP in model 1 (p = 0.048)(Fig. S2A), but this association attenuated after adjustments in model 2 (p = 0.109) (Fig. 3A). Paternal age <28 years of age was significantly associated with an increase of SGA in model 1 (p = 0.028) (Fig. S2B), but this association attenuated in model 2 (p = 0.092) (Fig. 3B).

4. Discussion

This is the first study investigating the association between paternal age and PV and uPVV in the first trimester of pregnancy. We hypothesized that older fathers would show smaller first trimester placental growth trajectories, because of potential aging-induced epigenetic alterations leading to dysregulation of paternally-expressed genes. However, no associations were shown in our study population between paternal age and first trimester PV or uPVV. Secondary, we found no associations between paternal age and the occurrence of HDP or SGA after adjusting for potential confounders.

Previous studies investigating paternal age and placental growth are limited and inconsistent and have only considered placental weight postpartum. Our study is in line with another study that found no association between paternal age and placental weight [35]. However, another study including almost 600,000 pregnancies found a higher placental weight in fathers aged >50 years as compared to fathers aged 20–24 years, but the absolute difference was small, especially after adjustment for potential confounders (range 6.8–14 g; 1–2% of placental weight) [11]. On the contrary, a 25% reduced placental weight was found in mice with advanced paternal age (11–15 months old) compared to mice with younger fathers (4–5 months old), but a comparable controlled setting is not possible in humans [12].

A proposed mechanism between paternal characteristics and placental growth is the sperm epigenome. DNA methylation patterns of imprinted genes are passed on to the offspring and paternally-expressed imprinted genes which are particularly expressed in the placenta largely stimulate placental growth [23,24,36]. Different preconceptional paternal exposures like nutrition have been found to impact imprinted genes in rodent placentas [21,37]. This indicates that paternal characteristics can affect epigenetic programming of the placenta and consequently placental growth and function. However, although significant changes in DNA methylation have been observed in sperm from older men, these alterations were generally found in non-imprinted regions and could therefore largely be removed during demethylation processes after fertilization, mitigating its potential effect on placental growth and explaining our negative results [25,26,38].

We hypothesized that paternal age has the largest effect early in pregnancy, because of accumulating effects of other factors influencing PV and uPVV development over gestation, but this was not observed in our study. Other factors, such as oocyte DNA and the maternal environment including nutrition can substantially impact placental growth already in the first trimester and especially in a tertiary hospital population, underlying parental conditions are suggested to have a more prominent effect on placental growth compared to paternal age [39,40]. Additionally, paternal age is strongly correlated with maternal age which has been shown to enhance placental growth [4]. Consequently, the effect of paternal age on PV/uPVV may be masked by other (maternal) factors already in early pregnancy.

(Early) placental growth is clinically important since aberrant growth is associated with adverse pregnancy outcomes, including fetal growth restriction and HDP [9,10]. Excluding pregnancies with HDP or SGA offspring did not change our outcomes in the sensitivity analysis. Additionally, we did not find an association between paternal age and the occurrence of SGA or HDP after adjustment for potential confounders, which is in line with other studies [13–15]. However, others reported U-shaped relationships where pregnancies with younger and/or older fathers showed an increased risk for hypertensive disorders [16–18,20] or low birth weight [15,19,20,41] and the largest effect was generally found for fathers aged >45 years. Since most of these studies comprised over a million couples, we would need a larger study population to detect such small differences. Additionally, differences between studies in statistical analysis including used age categories, the

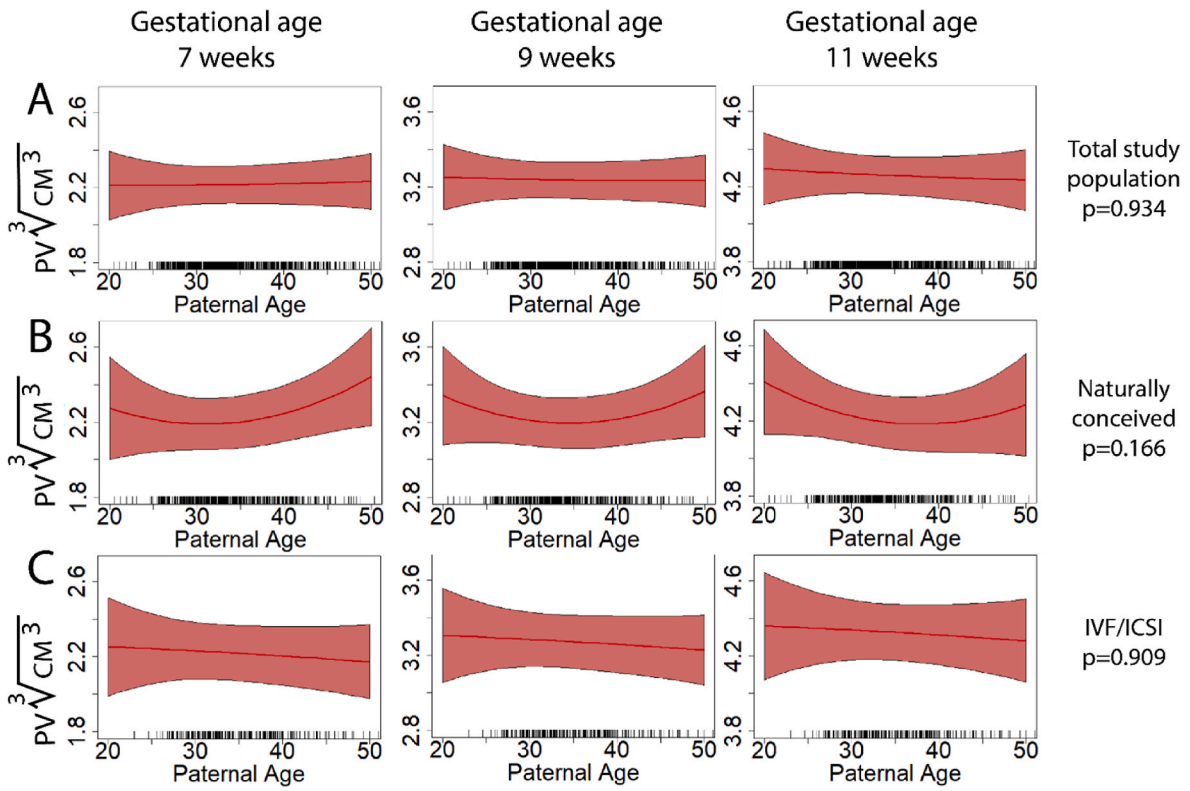

Fig. 2. Effect plots showing the relationship between paternal age and placental volume (PV) $\sqrt[3]{CM^3}$ at 7 weeks, 9 weeks and 11 weeks of gestation including 95% confidence intervals according to model 2. Rug plot at X-axis depicts the distribution of paternal age in our study population. Model adjusted for gestational age at the moment of the ultrasound, fetal sex, periconceptional parental smoking and maternal age, BMI, education and parity. P-values are outcomes of likelihood ratio test investigating the joined effect of paternal age, paternal age^2 and an interaction term including gestational age at the moment of the ultrasound and paternal age. A) The total study population; B) Naturally conceived pregnancies; C) pregnancies conceived via IVF/ICSI.

Table 2
Pregnancy outcomes in total study population with available delivery reports and stratified by paternal age categories.

Pregnancy outcome	Total (n = 1449)	<25 years (n = 47)	25–35 years (n = 775)	35–45 years (n = 544)	>45 years (n = 83)
HDP	139 (9.6)	4 (8.5)	80 (10.3)	51 (9.4)	4 (4.8)
PIH	81 (5.6)	1 (2.1)	51 (6.6)	26 (4.8)	3 (3.6)
PE	58 (4.0)	3 (6.4)	29 (3.7)	25 (4.6)	1 (1.2)
Gestational age at delivery	39 + 1 [38+0–40 + 1]	38 + 2 [37+4–39 + 4]	39 + 1 [38+1–40 + 1]	39 + 1 [37+6–40 + 1]	39 + 2 [38+3–40 + 4]
Missing	5	–	3	1	1
Birth weight (gram)	3340 [2965–3680]	3090 [2530–3600]	3340 [2960–3680]	3330 [2938–3690]	3420 [3088–3773]
Missing	*12*	–	7	3	2
SGA	182 (12.6)	12 (25.5)	98 (12.6)	65 (11.9)	7 (8.4)
Birth weight < p3	77 (5.3)	5 (10.6)	40 (5.2)	28 (5.1)	4 (4.8)
Missing	*20*	1	10	7	2

Data are presented as median [interquartile range (IQR)] or n (%). HDP = hypertensive disorder of pregnancy, PIH = pregnancy induced hypertension, PE = pre-eclampsia, SGA = small for gestational age (birth weight < p10), birth weight percentiles are according to Hoftiezer birth weight charts.

definition of low birth weight and handling of potential confounders could impact the results and explain parts of observed differences between studies.

4.1. Strengths and limitations

To our knowledge, this is the first study investigating the association between paternal age and PV and uPVV in the first trimester. One of the main strengths of this study is the use of standardized 3D ultrasound combined with VR to longitudinally assess early placental growth measurements in more than 800 pregnancies. These techniques are proven to be valid and well repeatable [27]. Other strengths of this study are the prospective design and our statistical approach. Although our model outcomes are more difficult to interpret as compared to linear regression models, our comprehensive models would allow for the identification of a non-linear relationship between paternal age and our studied outcomes, without categorizing paternal age which would inevitably lead to loss of information. Additionally, our models allow for the identification of a gestational-age dependent effect from paternal age on PV and uPVV. However, this study also has limitations. The effect estimates show that our study was not powered to find differences as small as found in a previous study conducted in humans [11] or to investigate the associations between paternal age and the risk of placental-related complications. Especially the number of fathers in our study population with more extreme ages is limited. For pregnancies with available ultrasound data, only 2.3% (n = 19) of fathers were <25 years old and 6.2% (n = 51) were 45+ years old. For pregnancies with available delivery reports to assess our secondary outcomes, 5.7% (n =

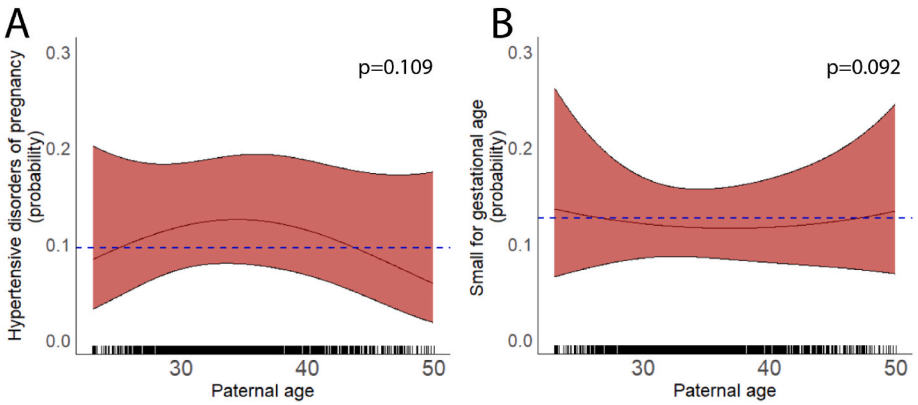

Fig. 3. Effect plots showing the relationship between paternal age and investigated pregnancy outcomes including 95% confidence intervals according to our adjusted model (model 2). Dotted blue line represents population average. Model input parameters: maternal age = 32.1 years, maternal BMI = 24.6, Parental smoking = no, fetal sex = boy (only for HDP), education level = intermediate, parity = nulliparous, mode of conception = naturally. P-values are outcomes of likelihood ratio test investigating the joined effect of paternal age and paternal age^2. Rug plot at X-axis depicts the distribution of paternal age in our study population. **A)** Hypertensive disorders of pregnancy (HDP) (p = 0.109), **B)** Small for gestational age (SGA) offspring (p = 0.092).

47) and 10.1% (n = 83) of fathers were aged <25 years old or 45+ years old, respectively. Although the paternal age distribution in our study is comparable to that in the general population, this hampers the robustness of our results for young and older fathers. Second, multiple factors including maternal adiposity, uterine position and embryonic movements can impact the quality of the ultrasound. Consequently, using our technical approach, 25–30% of PV and uPVV measurements are of insufficient quality and therefore not included in our analyses, limiting the number of (longitudinal) measurements [28]. Additionally, as for every observational study, residual confounding cannot be excluded. Our study population was enrolled at a tertiary hospital limiting generalizability of our results to the general population.

4.2. Conclusions

The clear trend of delayed fatherhood in many countries emphasizes the importance of investigating the potential impact of advanced paternal age on the course and outcome of pregnancy. In this study, we did not find a robust effect of paternal age on first trimester placental growth, utero-placental vascularization volume and placental-related pregnancy complications. Although accumulating evidence associates paternal conditions such as age to health and development of the offspring, underlying mechanisms might not mainly work through changes in placental (vascular) growth but rather through functional, histopathological changes, while changes in early placental growth might be smaller than what we could detect in our study. However, we provide reassuring evidence that paternal age, particularly between 25 and 45 years old, does not substantially impact placental growth in the first trimester in a tertiary care population. Future studies should validate our findings in the general population in larger cohorts, ideally including more fathers with a younger and advanced age.

Funding

This research was funded by the departments of Obstetrics and Gynaecology and Developmental Biology of the Erasmus Medical Centre, Rotterdam. This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

CRediT authorship contribution statement

M.M. Van Vliet: Data curation, Formal analysis, Investigation, Software, Writing – original draft. **S. Schoenmakers:** Supervision, Writing – review & editing. **B. Haug:** Investigation, Writing – review & editing. **S. Willemsen:** Formal analysis, Investigation, Methodology, Software, Supervision, Visualization, Writing – review & editing. **R.P.M. Steegers-Theunissen:** Conceptualization, Funding acquisition, Project administration, Supervision, Writing – review & editing.

Declaration of competing interest

None.

Acknowledgements

We thank all participants of The Rotterdam periconception cohort (Predict Study), without whom this study could not have been performed. We gratefully acknowledge the Predict study team for all efforts to recruit participants and collect data which contributed to the results of this study and Ann Vanrolleghem for data management and coordination. We especially thank Igna Reijnders and Eline de Vos for their efforts in the development, validation and measurement of PVs and uPVVs and Anton Koning for technical support.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.placenta.2024.03.009.

References

[1] J.A. Hutcheon, H. McNamara, R.W. Platt, A. Benjamin, M.S. Kramer, Placental weight for gestational age and adverse perinatal outcomes, Obstet. Gynecol. 119 (6) (2012) 1251–1258.
[2] C. Haavaldsen, S.O. Samuelsen, A. Eskild, Fetal death and placental weight/birthweight ratio: a population study, Acta Obstet. Gynecol. Scand. 92 (5) (2013) 583–590.
[3] V. Skirbekk, Delaying parenthood, for better and for worse, in: Book: Decline and Prosper! April, 2022, pp. 195–215.
[4] C. Haavaldsen, S.O. Samuelsen, A. Eskild, The association of maternal age with placental weight: a population-based study of 536,954 pregnancies, Bjog 118 (12) (2011) 1470–1476.
[5] S.C. Lean, H. Derricott, R.L. Jones, A.E.P. Heazell, Advanced maternal age and adverse pregnancy outcomes: a systematic review and meta-analysis, PLoS One 12 (10) (2017) e0186287.
[6] M.C. Magnus, A.J. Wilcox, N.H. Morken, C.R. Weinberg, S.E. Håberg, Role of maternal age and pregnancy history in risk of miscarriage: prospective register based study, BBmjmj 364 (2019) l869.
[7] H.M. Salihu, M.N. Shumpert, M. Slay, R.S. Kirby, G.R. Alexander, Childbearing beyond maternal age 50 and fetal outcomes in the United States, Obstet. Gynecol. 102 (5 Pt 1) (2003) 1006–1014.
[8] J. Cleary-Goldman, F.D. Malone, J. Vidaver, R.H. Ball, D.A. Nyberg, C. H. Comstock, G.R. Saade, K.A. Eddleman, S. Klugman, L. Dugoff, I.E. Timor-Tritsch, S.D. Craigo, S.R. Carr, H.M. Wolfe, D.W. Bianchi, M. D'Alton, F. Consortium, Impact of maternal age on obstetric outcome, Obstet. Gynecol. 105 (5 Pt 1) (2005) 983–990.

[9] R.P. Dahlstrøm B, P. Øian, L.J. Vatten, A. Eskild, Placenta weight in pre-eclampsia, Acta Obstet. Gynecol. Scand. 87 (6) (2008) 608–611.
[10] G.K. Sun C, C. Oyston, L.W. Chamley, A.R. Clark, J.L. James, The placenta in fetal growth restriction: what is going wrong? Placenta Jul 96 (2020) 10–18.
[11] E.M. Strøm-Roum, C. Haavaldsen, T.G. Tanbo, A. Eskild, Paternal age, placental weight and placental to birthweight ratio: a population-based study of 590,835 pregnancies, Hum. Reprod. 28 (11) (2013) 3126–3133.
[12] M.M. Denomme, J.C. Parks, B.R. McCallie, N.I. McCubbin, W.B. Schoolcraft, M. G. Katz-Jaffe, Advanced paternal age directly impacts mouse embryonic placental imprinting, PLoS One 15 (3) (2020) e0229904.
[13] L.B. Stern JE, M.D. Hornstein, H. Cabral, D. Gopal, H. Diop, M. Kotelchuck, The effect of father's age in fertile, subfertile, and assisted reproductive technology pregnancies: a population based cohort study, J. Assist. Reprod. Genet. 31 (11) (2017) 1437–1444. Nov.
[14] E.G. Hurley, E.A. DeFranco, Influence of paternal age on perinatal outcomes, Am. J. Obstet. Gynecol. 217 (5) (2017) 566 e1–e566 e6.
[15] B.V. Khandwala YS, G.M. Shaw, D.K. Stevenson, Y. Lu, M.L. Eisenberg, Association of paternal age with perinatal outcomes between 2007 and 2016 in the United States: population based cohort study, BMJ Oct 363 (31) (2018) k4372.
[16] N.E. Sartorius GA, Paternal age and reproduction, Hum Reprod Update. Jan-Feb 16 (1) (2010) 65–79.
[17] S. Harlap, O. Paltiel, L. Deutsch, A. Knaanie, S. Masalha, E. Tiram, L.S. Caplan, D. Malaspina, Y. Friedlander, Paternal age and preeclampsia, Epidemiology 13 (6) (2002) 660–667.
[18] T. Yu, T.S. Chen, F.W. Liang, P.L. Kuo, Does sex matter? Association of fetal sex and parental age with pregnancy outcomes in Taiwan: a cohort study, BMC Pregnancy Childbirth 20 (1) (2020) 348.
[19] P.S. Shah, b. Knowledge Synthesis Group on determinants of preterm/low birthweight, Paternal factors and low birthweight, preterm, and small for gestational age births: a systematic review, Am. J. Obstet. Gynecol. 202 (2) (2010) 103–123.
[20] A.P. Alio, H.M. Salihu, C. McIntosh, E.M. August, H. Weldeselasse, E. Sanchez, A. K. Mbah, The effect of paternal age on fetal birth outcomes, Am. J. Men's Health 6 (5) (2012) 427–435.
[21] G.M. Bhadsavle SS, Paternal epigenetic influences on placental health and their impacts on offspring development and disease, Front Genet Nov 13 (18) (2022) 1068408.
[22] B.h.D. Greenberg MVC, The diverse roles of DNA methylation in mammalian development and disease, Nat. Rev. Mol. Cell Biol. 20 (10) (2019) 590–607. Oct.
[23] M. Miozzo, G. Simoni, The role of imprinted genes in fetal growth, Biol. Neonate 81 (4) (2002) 217–228.
[24] X. Wang, D.C. Miller, R. Harman, D.F. Antczak, A.G. Clark, Paternally expressed genes predominate in the placenta, Proc. Natl. Acad. Sci. U. S. A. 110 (26) (2013) 10705–10710.
[25] T.G. Jenkins, K.I. Aston, D.T. Carrell, Sperm epigenetics and aging, Transl. Androl. Urol. 7 (Suppl 3) (2018) S328–S335.
[26] T.G. Jenkins, K.I. Aston, C. Pflueger, B.R. Cairns, D.T. Carrell, Age-associated sperm DNA methylation alterations: possible implications in offspring disease susceptibility, PLoS Genet. 10 (7) (2014) e1004458.
[27] I.F. Reijnders, A. Mulders, M.P.H. Koster, A.H.J. Koning, A. Frudiger, S. P. Willemsen, E. Jauniaux, G.J. Burton, R.P.M. Steegers-Theunissen, E.A. P. Steegers, New imaging markers for preconceptional and first-trimester utero-placental vascularization, Placenta 61 (2018) 96–102.
[28] M.A. Reijnders IF, M.P.H. Koster, A.T.M. Kropman, E.S. de Vos, A.H.J. Koning, S. P. Willemsen, M. Rousian, E.A.P. Steegers, R.P.M. Steegers-Theunissen, First-trimester utero-placental (vascular) development and embryonic and fetal growth: the Rotterdam periconception cohort, Placenta May 108 (2021) 81–90.
[29] M. Rousian, S. Schoenmakers, A.J. Eggink, D.V. Gootjes, A.H.J. Koning, M.P. H. Koster, A. Mulders, E.B. Baart, I.K.M. Reiss, J.S.E. Laven, E.A.P. Steegers, R.P. M. Steegers-Theunissen, Cohort Profile Update: the Rotterdam Periconceptional Cohort and embryonic and fetal measurements using 3D ultrasound and virtual reality techniques, Int. J. Epidemiol. 50 (5) (2021) 1426–1427l.
[30] R.P. Steegers-Theunissen, J.J. Verheijden-Paulissen, E.M. van Uitert, M. F. Wildhagen, N. Exalto, A.H. Koning, A.J. Eggink, J.J. Duvekot, J.S. Laven, D. Tibboel, I. Reiss, E.A. Steegers, Cohort profile: the Rotterdam periconceptional cohort (Predict study), Int. J. Epidemiol. 45 (2) (2016) 374–381.
[31] Gestational Hypertension and Preeclampsia: ACOG Practice Bulletin, Number 222, Obstet. Gynecol. 135 (6) (2020) e237–e260.
[32] E.A. Steegers, P. von Dadelszen, J.J. Duvekot, R. Pijnenborg, Pre-eclampsia, Lancet 376 (9741) (2010) 631–644.
[33] L. Hoftiezer, M.H.P. Hof, J. Dijs-Elsinga, M. Hogeveen, C. Hukkelhoven, R.A. van Lingen, From population reference to national standard: new and improved birthweight charts, Am. J. Obstet. Gynecol. 220 (4) (2019) 383 e1–e383 e17.
[34] C. Haavaldsen, T. Tanbo, A. Eskild, Placental weight in singleton pregnancies with and without assisted reproductive technology: a population study of 536,567 pregnancies, Hum. Reprod. 27 (2) (2012) 576–582.
[35] C. L'Abée, I. Vrieze, T. Kluck, J.J. Erwich, R.P. Stolk, P.J. Sauer, Parental factors affecting the weights of the placenta and the offspring, J. Perinat. Med. 39 (1) (2011) 27–34.
[36] N. Miyoshi, S.C. Barton, M. Kaneda, P. Hajkova, M.A. Surani, The continuing quest to comprehend genomic imprinting, Cytogenet. Genome Res. 113 (1–4) (2006) 6–11.
[37] P.I. Capobianco E, Paternal programming of fetoplacental and offspring metabolic disorders, S01434004, Placenta Jun 18 (23) (2023), 00144-3.
[38] C.T. Zeng Y, DNA methylation reprogramming during mammalian development, Genes 10 (4) (2019) 257. Mar 29.
[39] M.A. Reijnders IF, M. van der Windt, E.A.P. Steegers, R.P.M. Steegers-Theunissen, The impact of periconceptional maternal lifestyle on clinical features and biomarkers of placental development and function: a systematic review, Hum. Reprod. Update 25 (1) (2019) 72–94. Jan 1.
[40] S.S. Hoek J, B. Ringelberg, I.F. Reijnders, S.P. Willemsen, Y.B. De Rijke, A.G.M.G. J. Mulders, R.P.M. Steegers-Theunissen, Periconceptional maternal and paternal homocysteine levels and early utero-placental (vascular) growth trajectories: the Rotterdam periconception cohort, Placenta Nov 115 (2021) 45–52.
[41] X.K. Chen, S.W. Wen, D. Krewski, N. Fleming, Q. Yang, M.C. Walker, Paternal age and adverse birth outcomes: teenager or 40+, who is at risk? Hum. Reprod. 23 (6) (2008) 1290–1296.