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Foreword

We became interested in gynecology and assisted reproduction early in our study of medicine. Few studies have investigated the effect of paternal age on reproductive outcome. An improved understanding of this subject would be useful when counseling older couples who want to have children, both spontaneously and with the help of assisted reproduction.

We want to thank Signe Opdahl and Liv Bente Romundstad for guidance and help with our assignment.

Abstract

Studies investigating the role of increasing paternal age for neonatal health in pregnancies following assisted reproductive technology (ART) are limited. In this large cohort study, we evaluated the association between paternal age and preterm birth, SGA, perinatal death, gestational age and birth weight. We compared these associations between singleton pregnancies following spontaneous conception (SC) and ART conception (in vitro fertilization, IVF and intra-cytoplasmic sperm injection, ICSI). We used data from the Medical Birth Registry of Norway including 1 508 364 singleton births in the period 1988 to 2010. Each birth outcome was analyzed across paternal age as a continuous variable and categorical variable (25-29, 30-34, 35-39, 40-44, 45-49, 50-54 and ≥ 55). We used logistic and linear regression models and adjusted for maternal age, offspring sex, birth year, gestational age and parity. We found that the risk of SGA (OR 1.06, 95% CI 1.05 to 1.07) and perinatal death (OR 1.05, 95% CI 1.02 to 1.08) increased with five years increase in paternal age in SC pregnancies. For ART pregnancies, the risk of SGA was higher in pregnancies with paternal age between 30 and 44 years compared to 25 to 29 years (OR 1.34, 95% CI 0.91 to 1.95 for paternal age 40 to 44 years), but there were no clear trends across the range of paternal ages for any outcomes in ART pregnancies. In conclusion, increasing paternal age is not associated with increased risk of SGA, preterm birth, perinatal death, lower mean gestational age or mean birth SGA, preterm birth, perinatal death, lower mean gestational age or mean birth weight in ART pregnancies, but modestly associated with risk of SGA and perinatal death in SC pregnancies.

Background

Paternal age and reproductive outcomes

Over the last decades, delaying childbearing has become more common. The causes are multifactorial and the need for fertility treatment correlates with declining fertility following increasing age (Vassard, 2012). It is well known that advanced maternal age is a risk factor for adverse perinatal outcomes (Sagi-Dain, Sagi, & Dirnfeld, 2015). The risk of low birth weight, preterm birth and stillbirth increases with increasing maternal age (Alio et al., 2012). The influence of paternal factors on reproductive outcomes, including paternal age, is not as extensively studied. However, there are strong indications that advanced paternal age is associated with increased risk of severe conditions such as schizophrenia, autism specter disorders and several malignant diseases, including leukemia and breast cancer (Ramasamy, Chiba, Butler, & Lamb, 2015).

Alio et al. described a higher risk of stillbirth, low birth weight and preterm birth with increasing paternal age (Alio et al., 2012). However, Paulson et al. found no association between higher paternal age and adverse reproductive outcomes, in spite of reduced sperm count with increasing age (Paulson, Milligan, & Sokol, 2001). These studies have not distinguished between pregnancies following assisted reproductive technology (ART), and spontaneous conception (SC).

Changes in maternal and paternal age in the population

Maternal age is highly correlated with paternal age (Paulson et al., 2001). Over the last decades, the age of first-time parenthood has increased in Norway. In 1980, the mean age for women was 24.3 and for men 27.1 years, compared to 28.7 and 31.3 in 2014, respectively (Statistics Norway, 2016). Some of the reasons for the increased age of parenting are changes in women's roles in the society, advanced age of marriage and different socio-economic factors (Sharma et al., 2015) such as focus on education and career.

The use of Assisted Reproductive Technology (ART) in Norway

According to the Norwegian law of biotechnology, ART comprises fertilization outside the body and insemination. In insemination, sperm cells are inserted into the uterus by other methods than intercourse. ART is only permitted if the woman is married or in a non-marital cohabitation. It is a premise that the male and/or female is infertile, is a carrier of a severe genetic illness or that two women are married or living together in a non-marital cohabitation. The majority of couples in need of ART treatment are infertile or subfertile. According to the World Health Organization (WHO) definition, infertility is defined as lack of fertilization after one year of regular unprotected intercourses and subfertility as time to pregnancy > 1 year. Couples who need help of ART are in general older than couples that conceive spontaneously (Stern et al., 2014). The law does not state any upper limit for parental age and this vary between the fertility clinics, but there is a consensus between clinics in Norway that women over the age of 44 years should not be offered treatment. However, many women of younger age are not offered treatment because of limited chances for success. Prior to treatment, the couple has to give an informed consent. A clinician makes the final decision, based on medical and psychosocial considerations. The couple's capability to provide care for the desired child is emphasized (Norwegian law of Biotechnology, 2016, § 2-1 to 2-6)

In Norway, the first baby after assisted fertilization was born in 1984. So far, more than 30 000 children have been born as a result of ART in Norway. This accounts for approximately 1.5% of all births in Norway during this period. In recent years, nearly 5% of all births in Norway are a result of assisted reproduction. In 1984 five children were born after ART-treatment, compared to 2 039 in 2010.

In vitro fertilization (IVF) and intra-cytoplasmic sperm injection (ICSI)

In IVF, oocytes are harvested from the woman's ovary, and the conception takes place outside the body. For each oocyte retrieved, thousands of sperm cells are added. The fertilization process therefore resembles a spontaneous conception inside the woman's fallopian tube, with a selection of sperm cells reaching the oocyte and being able to penetrate the zona pellucida. The conception takes place under stabilized conditions in an incubator.

The fertilized oocyte requires about two to five days of maturation, and the best embryo is selected for transfer to the woman's uterus. The selection criteria are based on morphological kinetics of the first cleavage stages and development into blastocyst. After embryo replacement, the embryo can implant in the endometrial lining in the uterus.

ICSI is a fertilization method where a selected spermatozoa is injected into the oocyte by the use of a thin needle. This technique is called microinjection. ICSI is the preferred fertilization method when the sperm quality is impaired or if fertilization has failed in previous standard IVF treatment. Although ICSI has been developed mainly to overcome severe male infertility, the use of ICSI is now increasing because of its ability to increase the fertilization rate. Few negative effects on the offspring after ICSI have been described, but some studies indicate more major birth defects and an increased risk of chromosomal abnormalities in ICSI-children compared to children born after IVF (Ming, Yuan, Ping, Ping, & Jie, 2015). ICSI does not enhance natural selection in the same way IVF does (Begueria et al., 2014). For couples where male subfertility is the main cause for the couple's subfertility, the increased use of ICSI is beneficial. The success rate for ICSI in couples with no conceptions following IVF and intra-uterine insemination (IUI) is 11.4% (Brincat, Catania, Wismayer, & Calleja-Agius, 2015). Ming et al. found that IVF results in better fertilization rates than ICSI. In cases where the couple have a relatively low risk of fertilization failure, IVF is preferable to ICSI (Ming et al., 2015).

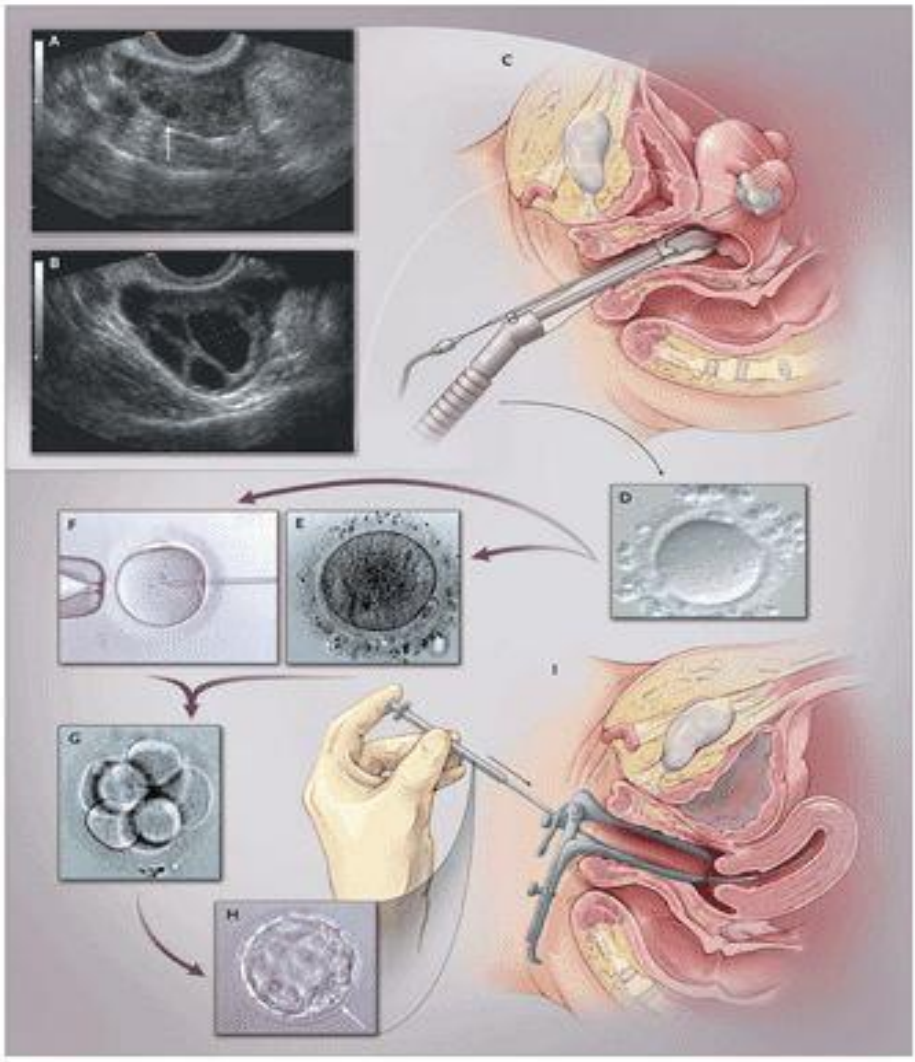

Figure 1. Flow chart of the procedures in assisted fertilisation. (Reprinted from New England Journal of Medicine, Van Voorhis BJ, Vol 356, jan 25, 2007 with permission from NEJM).

With increasing paternal age, sperm volume, motility and morphology decreases (Sartorius & Nieschlag, 2010). There is an association between reduced sperm quality and the ART method chosen. With poor sperm parameters, ICSI is the preferred method (Tomlinson, Lewis, & Morroll, 2013). One can therefore expect an association between paternal age and the use of ICSI in ART treatment. Whitcomb et al. have shown that the use of ICSI is increasing with advancing paternal age (Whitcomb et al., 2011).

Adverse reproductive outcomes following ART conceptions

In order to achieve high pregnancy rates, more than one embryo have been transferred to the uterus in each treatment cycle. This practice has led to high rates of twins and even higher

order multiples in ART pregnancies. Children born after ART have a generally higher risk of low birth weight and preterm birth and the higher rates of twin pregnancies explains a lion's share of the adverse perinatal outcomes in ART pregnancies (Pinborg et al., 2013). Elective single embryo transfer (eSET) is effective to avoid adverse outcomes associated to multiple pregnancies in ART (Bhattacharya & Kamath, 2014). For women under the age of 35, who receive IVF treatment, the success rate is higher when a single embryo is inserted (Kissin, Kulkarni, Kushnir, & Jamieson, 2014). Steinberg et al. recommended that eSET is practiced for women 35 to 37 years and couples with male infertility factor, in addition to women < 35 years that are today's guidelines (Steinberg, Boulet, Kissin, Warner, & Jamieson, 2013). Effective cryopreservation programs have been developed, and eSET, possibly followed by additional frozen-thawed cycles, have shown live birth rates similar to double embryo transfer (DET) following one stimulation (Bhattacharya & Kamath, 2014). The rates of multiple births have been reduced both in the USA (Bhattacharya & Kamath, 2014) and in Europe (European IVF-Monitoring Consortium (EIM); European Society of Human Reproduction and Embryology (ESHRE) et al., 2016). According to the latest reports, the twin rates in Europe are lingering around 20%. This reduction is explained by eSET and improved results after frozen/thawed cycles. However, there is still huge variations between different European countries (European IVF-Monitoring Consortium (EIM); European Society of Human Reproduction and Embryology (ESHRE) et al., 2016). It is well documented that singletons born after ART have an increased risk of adverse perinatal outcomes compared to singletons born after spontaneous conception (Pinborg et al., 2013). Partly, the increased risk is explained by parental factors (Romundstad et al., 2008), although a contribution from ART methods has so far not been excluded.

The contribution of maternal characteristics to the risk of adverse reproductive outcome is well studied unlike the paternal contribution. Maternal contributions such as nutrition, body mass index (BMI), smoking, age and vitamin supplement use affect fetal development in the peri-conception period in ART pregnancies (Steegers-Theunissen). Klonoff-Cohen and Robertshaw found a decreasing live birth rate with increasing paternal age after ART (Klonoff-Cohen & Natarajan, 2004; Robertshaw, Khoury, Abdallah, Warikoo, & Hofmann, 2014) while others show no clear association (Basso & Wilcox, 2006).

Potential clinical impact of an association between paternal age and adverse outcomes in ART pregnancies

Few studies have investigated the effect of paternal age on reproductive outcome in ART pregnancies. In contrast, increasing maternal age has a known negative effect on reproductive outcome (Sagi-Dain et al., 2015). An improved understanding of the association of paternal age on reproductive outcomes would be useful when counseling older couples who want to have children, both spontaneously and with the help of assisted reproduction. It would also be useful information for younger couples that are considering postponing family planning. An improved understanding of the association of paternal age on reproductive outcomes could be helpful to decide a cutoff age that ART-clinics can recommend for men.

Materials and methods

Study population and data sources

This study is a population based cohort study. The data were collected from the Medical Birth Registry of Norway and the IVF-registry from the period 1984 to 2010. The total number of singletons in this period was 1 508 364 in Norway, whereas 15 135 of these births were a result of ART. We obtained information about maternal and paternal age, maternal parity, fertilization method (spontaneous and IVF/ICSI), birthweight, gestational age and health of the child at birth. In this study, we only assessed singleton pregnancies, as multiple pregnancies require a different approach. We also excluded (successively): births before 1988 (n=202 591), missing values on gestational age (n=62 033), weight (n=1452) and offspring sex (n=508). Paternal age below 25 years (n=102 728), births in mothers younger than 20 years (n=6255) and older than 44 years (n=1299), births with gestational age below 22 weeks (n=2066) or above 45 weeks (n=778), and birth weight over 7000 g (n=1) were also excluded (Figure 2). Excluding pregnancies with fathers younger than 25 years and mothers younger than 20 years or older than 44 years made the ART pregnancies and SC pregnancies more comparable in age. Deliveries with gestational age below 22 weeks or above 45 weeks, or with birth weight ≥7000 grams, were excluded because these are extreme values and therefore few and more likely to be incorrectly reported. Before 1988, the number of ART-pregnancies was too small to provide reliable estimates. After excluding these, our study population consisted of 1 128 653 births. Preterm birth was defined as birth earlier than 37 weeks of gestation. Small for gestational age (SGA) was defined as weight at birth < -2 standard deviations (SDs), as estimated based on Marsál's formulas (Marsal et al., 1996). We defined perinatal death as stillbirth and early neonatal mortality (death within the first week after birth) (Norrman, Bergh, & Wennerholm, 2015).

Ethical considerations

Permission was granted from the regional ethics committee in northern Norway (REK 2010/1909-11).

Statistical analysis

The association between paternal age and preterm birth, being born small for gestational age and perinatal death was estimated using logistic regression. The association between paternal age and birth weight and gestational age was estimated using linear regression. Precision of the associations was estimated by calculating 95% confidence intervals (Cis). The associations between paternal age and birth outcome was studied both for categories of paternal age (25-29 years, 30-34 years, 35-39 years, 40-44 years, 45-49 years, 50-54 years, ≥ 55 years, or ≥ 50 years when comparing IVF and ICSI- pregnancies) and paternal age as a continuous variable (estimates calculated per five years increase in paternal age). Both relative and absolute differences were estimated to compare the importance of paternal age between spontaneous and ART pregnancies. The same approach was used for the comparison of IVF and ICSI pregnancies.

We adjusted for potentially confounding factors based on prior knowledge. Since maternal and paternal ages are closely correlated, we adjusted carefully for maternal age in two different analyses: First, in the total study sample, by including maternal age in five years categories as a covariate. Second, in a sample restricted to pregnancies with maternal age between 28 and 41 years, with adjustment for maternal age in two-year categories.

In all analyses, we also adjusted for parity, the child's sex, and birth year. We adjusted for parity because of increasing birth weight with increasing parity (Gaillard et al., 2014). We also restricted the analyses to pregnancies in nulliparous women, because of similarities between children of the same mother. We adjusted for the child's sex because boys on average have a higher weight (Wilbaux et al., 2016) and a lower gestational age at birth compared to girls (Vatten & Skjaerven, 2004). We adjusted for birth year to take into account temporal changes in several of the included factors: Since the 1950s through the 1990s mean birth weight has increased among singletons born at term, whereas in later years, mean birth weight has declined in spite of an increasing proportion of overweight and obese women (Catov, Lee, Roberts, Xu, & Simhan, 2015). Also, ART and other medical procedures have evolved since 1988 (Marianowski, Dabrowski, Zygula, Wieglos, & Szymusik, 2016). When assessing mean birth weight we adjusted for gestational age in addition to the factors previously mentioned, because of the close relation between pregnancy duration and fetal growth. We used a robust variance estimator to account for correlation within fathers in all analyses. All analyses were done using Stata MP, version 12.

Results

In our population, the mean parental age for men and women who conceived spontaneously was 33.2 (SD 5.4) and 30.0 (SD 4.7) years, respectively. Couples who conceived using ART were in average a few years older, with paternal age 36.4 (SD 5.4) and maternal age 33.5 (SD 3.9) years. Table 1 and 2 summarize the characteristics of the total study population, SC and ART (IVF, ICSI) pregnancies. Parity was lower in ART pregnancies compared to SC pregnancies. For example, in 65.4% of ART pregnancies, the mother was nulliparous, compared to 37.2% in spontaneously conceived pregnancies. Children born after ART had 126 grams lower mean birth weight and were more frequently born preterm compared to children born after spontaneous conception. In ART pregnancies, 8.4% were born in weeks 28 to 36, in contrast to 5.0% the SC pregnancies. The proportion of perinatal death was 0.8% in ART pregnancies, compared to 0.5% in SC pregnancies.

SGA

In SC pregnancies, we found a higher risk of SGA with increasing paternal age. The highest risk was observed for paternal age ≥ 55 years with an absolute risk of 5.7% and an OR of 1.45 (95% CI 1.24 to 1.71) compared to the age group between 25 and 29 years (table 3). In all ART pregnancies combined, the risk of SGA tended to increase with paternal age up to the age of 44 years and decreased from 55 years. Similar results were obtained when restricting analyses to pregnancies in nulliparous women (table 5) and when adjusting for maternal age in two-year categories (table 7). No clear differences were found in separate analyses of the IVF and ICSI pregnancies (table 4, 6, 8).

When handling paternal age as a continuous variable, every five years increase in paternal age increased the odds of SGA by 6% for the SC pregnancies (OR 1.06, 95% CI 1.05 to 1.07), while no clear trend was found in the analysis restricted to all ART pregnancies combined, (OR 0.98, 95% CI 0.91 to 1.05. The association of paternal age with SGA outcome was different for all ART pregnancies combined compared to SC births ($P_{interaction}$ 0.017) (Table 3). Similarly we found no clear associations when subdividing ART into IVF and ICSI (OR per five years increase in paternal age 0.94, 95% CI 0.85 to 1.05 and OR 1.05, 95% CI 0.94 to 1.78, for IVF and ICSI, respectively) (table 4).

Preterm birth

In all pregnancies combined, the risk of preterm birth was lower in pregnancies with paternal age between 30 and 39 years compared to pregnancies with both younger and older fathers. In analysis restricted to the SC pregnancies, we found a similar pattern. For all ART pregnancies combined, we found no substantial association between paternal age in categories and preterm birth (Table 3). For paternal age ≥ 55 years, 6.2% of children born after SC pregnancies are preterm, while 12.6% are born preterm after ART pregnancies. Restricting the analyses to pregnancies in nulliparous women and adjusting for maternal age in two-year categories did not change this impression (table 7). Similarly, for ICSI and IVF, we found no substantial associations (table 8).

With age as a continuous variable, every five years increase in paternal age increased the odds of preterm birth in SC pregnancies (OR 1.02, 95% CI 1.01 to 1.03), and a slightly decreased odd of preterm birth in all ART pregnancies combined (OR 0.96, 95% CI 0.90 to 1.03). The associations were statistically significantly different, $P_{interaction}$ 0.01 (table 3). When restricting the analyses to pregnancies in nulliparous women and when adjusting for maternal age in two-year categories, the increase in the SC pregnancies and the decrease in the ART pregnancies were less evident. Furthermore, we found a negative association in the ICSI pregnancies, and no substantial association in the IVF pregnancies, however, the statistical evidence for a difference between these findings was weak, $P_{interaction}$ 0.4 (table 4). Similar results were obtained when restricting to pregnancies in nulliparous women and when adjusting for maternal age in two-year categories (table 5, 6, 7 and 8).

Perinatal death

There was an increased risk of perinatal death in SC pregnancies in the age categories between 30 and 54 years, compared to paternal age group below 29 years of age (table 3). For pregnancies in nulliparous women, we observed the same tendency (table 5). After adjustment for maternal age in two-year categories, the risk increased for paternal age groups ≥ 30 years old (table 7).

There was no clear association with paternal age in all ART pregnancies combined (table 3). The findings for pregnancies in nulliparous women in ART pregnancies were inconclusive,

with varying results and broad confidence intervals (table 5). This also applied for pregnancies with adjustment for maternal age in two-year categories (table 7).

With five years increase in paternal age in SC pregnancies the risk increased for perinatal death, OR 1.05 (95% CI 1.01 to 1.08), while there was no clear association in ART pregnancies, OR 0.91 (95% CI 0.74 to 1.13). However, the associations were not statistical significantly different between SC and ART pregnancies (table 3). For pregnancies in nulliparous women and with adjustment for maternal age in two-year categories, we found the same pattern (table 5 and 7).

Mean birth weight

We found a decreasing birth weight with increasing paternal age in SC pregnancies. With paternal age ≥ 55 years, children weighed on average 45.9 grams less (95% CI -64.4 to -27.3) compared to the reference group (paternal age 25-29 years), in SC pregnancies (table 9). When restricting the analyses to pregnancies in nulliparous women and with adjustment for maternal age in two-year categories, the same tendency was found (table 11 and 13). With five years increase in paternal age there was a slight decrease in birth weight in SC pregnancies (table 9). The same tendency was found for pregnancies in nulliparous women while no association in ART pregnancies, indicating that the associations differed between the SC and ART pregnancies ($P_{interaction}$ 0.003) (table 11). When adjusting for maternal age in two-year categories, and comparing the SC pregnancies with the all ART pregnancies combined, results were similar as in the overall analysis (table 13).

When investigating IVF and ICSI pregnancies separately, there were also no clear associations. The results were inconclusive and confidence intervals wide (table 10, 12 and 14).

Mean gestational age

In the total population and SC pregnancies, the gestational age decreased with nearly one day when paternal age was ≥ 55 years, compared to the reference group (table 9). The same tendency was found when restricting the analyses to pregnancies in nulliparous women (table 11). However, when restricting the analysis to pregnancies with adjustment for maternal age in two-year categories, the association with paternal age attenuated completely (table 13).

In all ART pregnancies combined, and when separating IVF and ICSI pregnancies, there was no clear association between paternal age and gestational age (table 9 and 10). In the subsample of pregnancies in nulliparous women, there was a statistically significant difference between SC pregnancies and all ART pregnancies combined when comparing the effect of five years increase in paternal age on gestational age (table 11). When adjusting for maternal age in two-year categories, we found that paternal age was not associated with gestational age (table 13).

Discussion

In this large cohort study, we evaluated the association of paternal age with preterm birth, SGA, perinatal death, gestational age and birth weight. We compared these associations between pregnancies following spontaneous conception and mode of ART-conception (IVF and ICSI). We found a higher risk of SGA with increasing paternal age and a weak, but clear association between perinatal death and increasing paternal age in SC pregnancies. There was no increase in risk of SGA and perinatal death with advancing paternal age in ART pregnancies. There was a generally increased risk of preterm birth after ART compared to SC pregnancies, but no association in either group with paternal age after careful adjustment for maternal age. We found a decrease in birth weight with increasing paternal age in SC pregnancies, but the same pattern was not found in ART pregnancies combined. There was no clear association between increasing paternal age and gestational age.

Comparison with previous studies

In our sample, we found a higher maternal and paternal age in ART pregnancies compared to SC pregnancies, and lower parity among ART mothers compared to mothers who conceived after spontaneous conception. This is in line with previous studies from other countries (Stern et al., 2014) (Stephen, Chandra, & King, 2016).

Alio et al described a lower risk of SGA in SC pregnancies when paternal age was ≥ 30 years compared to the reference group (25-29 years) (Alio et al., 2012). Both Romundstad et al and Pinborg et al found an increased risk of SGA after ART compared to children born after spontaneous conception (Pinborg et al., 2013; Romundstad et al., 2008). However, Romundstad found that the difference between ART and SC pregnancies was smaller when comparing siblings where one was conceived spontaneously and the other with help of ART (sib-ship analyses) (Romundstad et al., 2008).

Stern et al and Basso et al did not find an association between advancing paternal age and preterm birth (Basso & Wilcox, 2006) (Stern et al., 2014). Alio et al and Sharma et al found an increased risk of preterm birth with increasing paternal age (Alio, 2012) (Sharma et al., 2015). Pinborg et al found an increased risk of preterm birth in ART pregnancies, also when comparing siblings where one was conceived spontaneously and the other with help of ART.

Pinborg et al discussed whether this could be attributed to hormone stimulation and/or ART-techniques (Pinborg et al., 2013). Romundstad et al found an increased risk of preterm birth in ART pregnancies, but no difference in the sibling-relationship comparison, which implies that the increased risk may not be explained by ART treatment factors alone (Romundstad et al., 2008). A reason for the decreased risk in the ART pregnancies with higher paternal age could be that the couples are meticulously selected for ART treatment, and therefore are in good health, despite their fertility issues.

A possible explanation for the increase in risk of perinatal death with advancing paternal age in SC pregnancies could be a decline in paternal health and sperm quality, which may affect the birth outcome. The low risk of perinatal death when paternal age was ≥ 55 years was not present in sensitivity analyses. Reasons for this could be that the low risk was due to maternal factors or that we had too few observations in the category paternal age ≥ 55 years. Paulson et al did not find an association between increasing paternal age and live birth rates (Paulson et al., 2001), while Robertshaw et al found a reduced live birth rate with advancing paternal age (Robertshaw et al., 2014). Both studies used the oocyte donation model. Several other studies describe an increased risk of stillbirth with increasing paternal age after adjusting for maternal age (Alio et al., 2012) (Sharma et al., 2015). In ART pregnancies, the risk of perinatal death was increased between paternal ages 30 to 45 years.

Klonoff-Cohen et al did not find a statistically significant association between paternal age and low birth weight after ART pregnancies (Klonoff-Cohen & Natarajan, 2004). Romundstad et al and Pinborg et al found an increased risk of reduced mean birth weight after ART compared to children born after spontaneous conception, but they did not consider increased paternal age in their studies (Romundstad et al., 2008) (Pinborg et al., 2013).

We found a low risk of SGA with paternal age above 55 years and of perinatal death with paternal age above 45 years in ART pregnancies, although not statistically significant compared to the reference group. This is possibly a reflection of selection of healthy couples by ART-clinics and a selection of healthy partner by the woman. A Norwegian report from 2011 showed that the percentage of childless men has increased. Men with low and high socioeconomic status have a tendency to have children with more than one partner. An explanation for this could be that men with low socioeconomic status have more unstable partnerships, while men with higher socioeconomic status are thought of as good potential

fathers (Lappegård & Rønsen, 2011). Another explanation for our results could be that the sample size for fathers ≥ 45 years is small. Klonoff-Cohen et al found a lower live birth rate with increasing paternal age after ART pregnancies (Klonoff-Cohen & Natarajan, 2004).

Strengths and limitations of the study

The large sample size of the current study enabled a precise estimation of the association between paternal age and adverse neonatal outcomes in SC pregnancies. However, statistical power was limited in analyses in ART pregnancies, especially when investigating IVF and ICSI pregnancies separately. We have adjusted for important confounding factors such as maternal age and parity.

Another strength in our study is the amount of information that is available the Norwegian Birth Registry. Our results are representative to the Norwegian population as reporting to the registry is mandatory and therefore expected to be unselected. We therefore consider selection bias as an unlikely explanation for the findings.

Our study also has some weaknesses. We could not adjust for income, education, alcohol intake or smoking habits of the parents, because this information was not available. One can assume that parents with higher education have more knowledge about a healthy lifestyle and more often follow a healthy diet, exercise, avoid smoking, and have a favorable BMI etc. Lifestyle may affect the reproductive outcome (Zeinab, Zohreh, & Samadaee Gelehkolaee, 2015). We cannot conclude whether or not the effect on birth outcomes with increasing paternal age is due to the increasing paternal age, the poor sperm quality with high paternal age or a combination of both.

Paternal age is strongly correlated to maternal age. To eliminate the influence of maternal age, some studies have used the oocyte donation model. The oocyte donation model has some advantages when studying the association of paternal age on reproductive outcomes using ART. The use of oocytes from young donors bypasses the age related effect of DNA damage on oocytes in women with advanced age. The women donating oocytes are typically young women and the women receiving the oocyte do not have to undergo ovarian

hyperstimulation, which may affect the receptivity and embryo development (Sagi-Dain et al., 2015). However, the oocyte donation model does not eliminate any potential influences of age on the physiology of the recipient woman during pregnancy. Oocyte donation is not permitted in Norway (Norwegian law of Biotechnology, 2016, §2-18), therefore we were not able to investigate this association. Women, who get fertilization treatment abroad, may have been registered as SC pregnancies rather than ART pregnancies. This also accounts for women who get pregnant after oocyte donation abroad, but they constitute a negligible share of the SC pregnancies. Even though we adjusted for maternal age in two-year categories, we cannot exclude any residual confounding by maternal age.

The outcome in ART pregnancies may be influenced by the technology, which develops constantly. Stimulation protocols, laboratory procedures and the use of frozen/thawed-cycles change over time (European IVF-Monitoring Consortium (EIM); European Society of Human Reproduction and Embryology (ESHRE) et al., 2016) (Farquhar, Rishworth, Brown, Nelen, & Marjoribanks, 2015). Therefore, it will be beneficial to do future studies on the subject.

Conclusion

The risk of SGA, perinatal death and low birth weight is higher with advanced paternal age in spontaneous pregnancies. We did not find an association between higher paternal age and adverse outcomes in ART pregnancies. A possible explanation for our findings could be that the careful selection of couples that receive ART treatment compensate for a potentially negative effect of advancing paternal age.

Our findings can be useful when counseling couples that consider delaying childbearing, but do not give reason to change guidelines with regard to male age limits in ART-clinics. We did not find any clear associations of paternal age on adverse reproductive outcomes after ART pregnancies. However, this does not exclude an effect of paternal age. More couples delay parenting and the number of children born after ART is increasing, therefore more studies on the association of paternal age on reproductive outcome after ART are needed.

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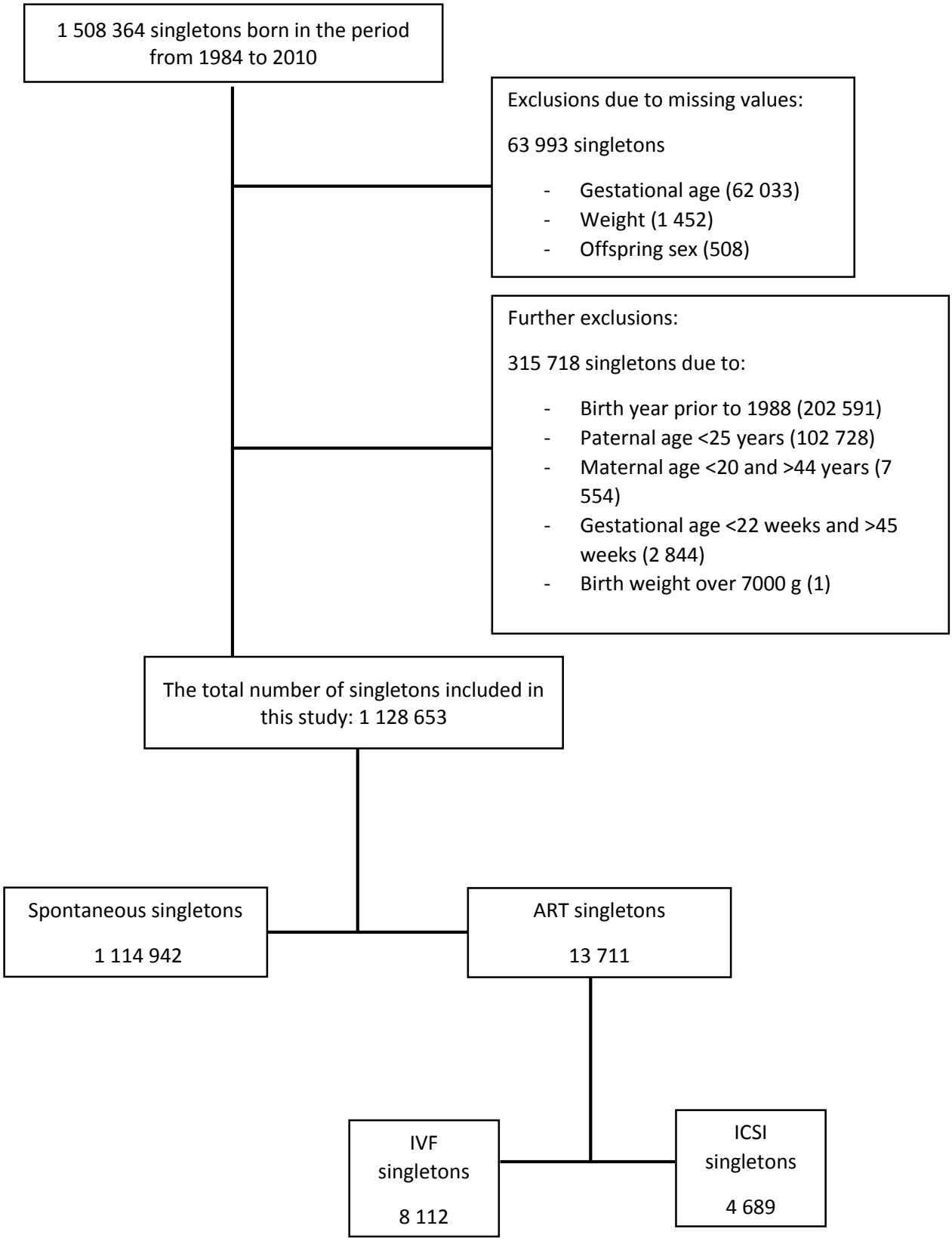

Figure 2. Overview of study population and exclusions

TABLE 1: PARENTAL CHARACTERISTICS OF THE INCLUDED SINGLETON PREGNANCIES

	TOTAL		SC		All ART combined		IVF		ICSI	
NUMBER OF OBSERVATIONS	1 128 653		1 114 942		13 711		8112		4689	
PATERNAL AGE (MEAN,SD)	33.2	5.5	33.2	5.4	36.4	5.4	36.1	5.2	36.7	5.8
PATERNAL AGE, CATEGORIES										
25-29	310 898	27.6	309 838	27.8	1 060	7.7	634	7.8	355	7.6
30-34	417 975	37.0	413 630	37.1	4 345	31.7	2 634	32.5	1 449	30.9
35-39	261 330	23.2	256 329	23.0	5 001	36.5	3 020	37.2	1 662	35.4
40-44	98 015	8.7	95 721	8.6	2 294	16.7	1 316	16.2	802	17.1
45-49	28 918	2.6	28 220	2.5	698	5.1	376	4.6	266	5.7
50-54	8 244	0.7	8 033	0.7	211	1.5	89	1.1	105	2.2
≥ 55	3 273	0.3	3 171	0.3	102	0.7	43	0.5	50	1.1
MATERNAL AGE (MEAN,SD)	30.0	4.7	30.0	4.7	33.5	3.9	33.7	3.9	33.22	4.0
MATERNAL AGE CATEGORIES										
20-24	133 647	11.8	133 524	12.0	123	0.9	63	0.8	48	1.0
25-29	405 161	35.9	403 032	36.2	2 129	15.5	1 145	14.1	827	17.6
30-34	390 215	34.6	384 464	34.5	5 751	41.9	3 438	42.4	1 967	42.0
35-39	169 430	15.0	164 516	14.8	4 914	35.8	3 012	37.1	1 600	34.1
40-44	30 200	2.7	29 406	2.6	794	5.8	454	5.6	247	5.3
PARITY (N, %)										
0	423 925	37.6	414 953	37.2	8 971	65.4	5 269	65.0	3 065	65.4
1	422 677	37.5	418 843	37.6	3 834	28.0	2 305	28.4	1 307	27.9
2	202 650	18.0	201 944	18.1	706	5.2	419	5.2	251	5.4
3	55 706	4.9	55 553	5.0	153	1.1	87	1.1	54	1.2
≥ 4	23 696	2.1	23 649	2.1	47	0.3	32	0.4	12	0.3

Abbreviations: SC – spontaneous conception, ART - assisted reproductive technology, IVF- in vitro fertilization, ICSI- intra-cytoplasmic sperm injection, SD- standard deviation, N - number.

TABLE 2: NEONATAL CHARACTERISTICS OF THE INCLUDED SINGLETONS

	TOTAL		SC		All ART combined		IVF		ICSI	
NUMBER OF OBSERVATIONS	1 128 653		1 114 942		13 711		8 112		4 689	
BIRTH WEIGHT(MEAN, SD)	3562	585	3564	584	3438	652	3420	658	3466	640
GESTATIONAL AGE (N, %)										
22-27	3 948	0.4	3 863	0.4	85	0.6	52	0.6	26	0.6
28-36	56 661	5.0	55 508	5.0	1 153	8.4	741	9.1	349	7.4
37	49 310	4.4	48 497	4.4	813	5.9	479	5.9	277	5.9
38	125 904	11.2	124 214	11.1	1 690	12.3	1 032	12.7	569	12.1
39	241 538	21.4	238 604	21.4	2 934	21.4	1 777	21.9	985	21.0
40	312 085	27.7	308 558	27.7	3 527	25.7	1 989	24.5	1 298	27.7
41	225 624	20.0	223 099	20.0	2 525	18.4	1 453	17.9	877	18.7
42	93 875	8.3	92 976	8.3	899	6.6	532	6.6	288	6.4
≥ 43	19 708	1.9	19 623	1.8	85	0.6	57	0.7	20	0.4
PERINATAL DEATH (N, %)										
NO	1 122 916	99.5	1 109 304	99.5	13 612	99.3	8052	99.3	4659	99.4
YES	5737	0.5	5638	0.5	99	0.8	60	0.7	30	0.6
SEX (N, %)										
BOY	579 846	51.4	572 793	51.4	7053	51.4	4279	52.8	2333	49.8
GIRL	548 807	48.6	542 149	48.6	6658	48.6	3833	47.3	2356	50.3

Abbreviations: SC – spontaneous conception, ART - assisted reproductive technology, IVF- in vitro fertilization, ICSI- intra-cytoplasmic sperm injection, SD- standard deviation, N- number.

TABLE 3: ASSOCIATION OF PATERNAL AGE WITH ADVERSE NEONATAL OUTCOMES, ACCORDING TO CONCEPTION METHOD

		Total			Spontaneous conception			All ART combined			
	Paternal age	**Risk (%)**	**OR[1]**	**95 % CI[2]**	**Risk (%)**	**OR[1]**	**95 % CI**	**Risk (%)**	**OR[1]**	**95% CI**	**P interaction**
SGA	*25-29*	4.0	1	ref	4.0	1	ref	4.5	1	ref	
	30-34	4.0	1.01	0.98 to 1.03	4.0	1.01	0.98 to 1.03	5.5	1.24	0.89 to 1.73	
	35-39	4.2	1.05	1.02 to 1.09	4.2	1.05	1.02 to 1.09	5.5	1.25	0.88 to 1.77	
	40-44	4.8	1.22	1.17 to 1.27	4.8	1.21	1.16 to 1.27	5.9	1.34	0.91 to 1.95	
	45-49	5.0	1.27	1.19 to 1.35	5.0	1.28	1.20 to 1.36	4.8	1.07	0.66 to 1.73	
	50-55	4.9	1.23	1.11 to 1.38	4.9	1.25	1.12 to 1.39	4.1	0.91	0.43 to 1.90	
	≥ 55	5.5	1.40	1.20 to 1.64	5.7	1.45	1.24 to 1.71	0.01	0.20	0.03 to 1.49	
	Per 5 years increase		1.06	1.05 to 1.07		1.06	1.05 to 1.07		0.98	0.91 to 1.05	0.13
PRETERM BIRTH	*25-29*	5.5	1	ref	5.5	1	ref	9.7	1	ref	
	30-34	5.2	0.95	0.92 to 0.97	5.1	0.94	0.92 to 0.96	10.4	1.08	0.85 to 1.37	
	35-39	5.3	0.97	0.94 to 0.99	5.3	0.97	0.94 to 0.99	8.1	0.82	0.63 to 1.05	
	40-44	5.5	1.01	0.97 to 1.05	5.5	1.01	0.97to 1.05	8.2	0.83	0.62 to 1.10	
	45-49	6.1	1.12	1.06 to 1.18	6.1	1.12	1.06 to 1.18	9.4	0.97	0.68 to 1.37	
	50-55	6.2	1.14	1.04 to 1.24	6.2	1.15	1.05 to 1.26	7.9	0.80	0.46 to 1.38	
	≥ 55	6.3	1.17	1.00 to 1.33	6.2	1.39	0.98 to 1.32	12.6	1.34	0.71 to 2.55	
	Per 5 years increase		1.02	1.01 to 1.03		1.02	1.01 to 1.03		0.96	0.90 to 1.03	0.01
PERINATAL DEATH	*25-29*	0.5	1	ref	0.5	1	ref	0.5	1	ref	
	30-34	0.5	1.00	0.92 to 1.08	0.5	0.99	0.92 to 1.07	0.9	1.61	0.62 to 4.19	
	35-39	0.5	1.09	0.99 to 1.19	0.5	1.08	0.99 to 1.19	0.7	1.24	0.44 to 3.48	
	40-44	0.6	1.17	1.04 to 1.31	0.6	1.16	1.03 to 1.30	0.9	1.63	0.56 to 4.80	
	45-49	0.6	1.17	1.00 to 1.38	0.6	1.19	1.01 to 1.40	0.4	0.73	0.17 to 3.16	
	50-55	0.6	1.29	0.98 to 1.70	0.6	1.31	0.99 to 1.73	0.4	0.79	0.09 to 6.98	
	≥ 55	0.4	0.85	0.51 to 1.42	0.4	0.88	0.53 to 1.47	-[2]	-[2]	-[2]	
	Per 5 years increase		1.05	1.02 to 1.08		1.05	1.02 to 1.08		0.91	0.74 to 1.13	0.36

[1]Adjusted for birth year, maternal age, parity, the child's sex.
[2]Too few observations.
Abbreviations: ART - assisted reproductive technology, OR- odds ratio, CI- confidence interval, SGA- small for gestational age.

TABLE 4: ASSOCIATION OF PATERNAL AGE WITH ADVERSE NEONATAL OUTCOMES, ACCORDING TO ART FERTILIZATION METHOD

		IVF			ICSI			
	Paternal age	**Risk (%)**	**OR**	**95% CI**	**Risk (%)**	**OR**	**95% CI**	**P interaction**
SGA	*25-29*	5.9	1	ref	2.1	1	ref	
	30-34	6.0	1.01	0.69 to 1.48	4.2	2.05	0.97 to 4.31	
	35-39	5.9	0.99	0.67 to 1.48	5.0	2.47	1.15 to 5. 29	
	40-44	5.8	0.98	0.62 to 1.54	6.1	3.07	1.38 to 6.32	
	45-49	4.2	0.69	0.37 to 1.30	4.8	2.36	0.94 to 5.92	
	≥ 50	4.3	0.71	0.29 to 1.75	1.8	0.86	0.22 to 3.37	
	Per 5 years increase		0.94	0.85 to 1.05		1.05	0.94 to 1.78	0.08
PRETERM BIRTH	*25-29*	10.3	1	ref	9.1	1	ref	
	30-34	10.7	1.04	0.78 to 1.40	9.8	1.08	0.69 to 1.69	
	35-39	9.0	0.86	0.63 to 1.17	6.8	0.72	0.45 to 1.16	
	40-44	9.1	0.87	0.61 to 1.24	7.7	0.83	0.50 to 1.40	
	45-49	9.9	0.96	0.61 to 1.51	9.0	0.98	0.54 to 1.79	
	≥ 50	0.1	1.39	0.77 to 2.50	4.7	0.49	0.21 to 1.13	
	Per 5 years increase		1.00	0.91 to 1.09		0.93	0.83 to 1.04	0.45

[1]Adjusted for birth year, maternal age, parity, the child's sex.
Abbreviations: IVF- in vitro fertilization, ICSI- intra-cytoplasmic sperm injection, OR- odds ratio, CI- confidence interval, SGA- small for gestational age.

TABLE 5: ASSOCIATION OF PATERNAL AGE WITH ADVERSE NEONATAL OUTCOMES, ACCORDING TO CONCEPTION METHOD. RESTRICTED TO PREGNANCIES IN NULLIPAROUS WOMEN.

		TOTAL		SC		All ART combined		
	Paternal age	**OR**	**95 % CI**	**OR**	**95 % CI**	**OR**	**95% CI**	**P interaction**
SGA	*25-29*	1	ref	1	ref	1	ref	
	30-34	1.05	1.02 to 1.09	1.05	1.02 to 1.09	1.29	0.90 to 1.84	
	35-39	1.16	1.11 to 1.21	1.16	1.11 to 1.34	1.18	0.81 to 1.72	
	40-44	1.27	1.19 to 1.34	1.26	1.19 to 1.34	1.33	0.87 to 2.01	
	45-49	1.16	1.05 to 1.27	1.17	1.06 to 1.29	1.03	0.59 to 1.79	
	50-55	1.08	0.92 to 1.27	1.08	0.92 to 1.28	1.01	0.46 to 2.24	
	≥ 55	1.33	1.07 to 1.66	1.40	1.12 to 1.75	0.26	0.04 to 2.01	
	Per 5 years increase	1.06	1.04 to 1.07	1.06	1.04 to 1.07	0.98	0.90 to 1.06	0.017
PRETERM BIRTH	*25-29*	1	ref	1	ref	1	ref	
	30-34	0.97	0.94 to 1.00	0.96	0.93 to 0.99	1.19	0.90 to 1.57	
	35-39	0.99	0.95 to 1.03	0.99	0.95 to 1.03	0.93	0.69 to 1.25	
	40-44	1.00	0.94 to 1.06	1.00	0.94 to 1.06	0.88	0.63 to 1.24	
	45-49	1.05	0.96 to 1.15	1.06	0.96 to 1.16	0.90	0.57 to 1.41	
	50-55	1.06	0.91 to 1.23	1.07	0.92 to 1.25	0.87	0.45 to 1.66	
	≥ 55	1.09	0.88 to 1.35	1.05	0.84 to 1.32	1.52	0.70 to 3.31	
	Per 5 years increase	1.01	0.99 to 1.02	1.01	0.99 to 1.02	0.93	0.86 to 1.01	0.002
PERINATAL DEATH	*25-29*	1	ref	1	ref	1	ref	
	30-34	1.02	0.91 to 1.14	1.01	0.91 to 1.13	1.66	0.57 to 4.83	
	35-39	1.09	0.95 to 1.26	1.09	0.95 to 1.26	1.49	0.48 to 4.59	
	40-44	1.09	0.90 to 1.33	1.05	0.86 to 1.29	2.13	0.65 to 7.02	
	45-49	1.11	0.82 to 1.51	1.15	0.85 to 1.56	0.88	0.16 to 4.86	
	50-55	1.38	0.88 to 2.17	1.42	0.90 to 2.25	1.21	0.13 to 11.38	
	≥ 55	0.44	0.14 to 1.37	0.47	0.15 to 1.47	-[2]	-[2]	
	Per 5 years increase	1.02	0.98 to 1.07	1.03	0.98 to 1.08	0.96	0.76 to 1.22	0.584

[1]Adjusted for birth year, maternal age, the child's sex.
[2] Too few observations.
Abbreviations: SC – spontaneous conception, ART - assisted reproductive technology, OR- odds ratio, CI- confidence interval, SGA- small for gestational age.

TABLE 6: ASSOCIATION OF PATERNAL AGE WITH ADVERSE NEONATAL OUTCOMES, ACCORDING TO ART FERTILIZATION METHOD. RESTRICTED TO PREGNANCIES IN NULLIPAROUS WOMEN.

		IVF		ICSI		
	Paternal age	**OR**	**95% CI**	**OR**	**95% CI**	**P interaction**
SGA[1]	*25-29*	1	ref	1	ref	
	30-34	0.99	0.66 to 1.49	2.05	0.96 to 4.37	
	35-39	0.86	0.55 to 1.33	2.25	1.02 to 4.95	
	40-44	0.99	0.60 to 1.61	2.67	1.15 to 6.23	
	45-49	0.85	0.43 to 1.68	1.40	0.46 to 4.27	
	≥ 50	0.69	0.26 to 1.84	1.02	0.25 to 4.12	
	Per 5 years increase	0.95	0.85 to 1.07	1.03	0.90 to 1.18	0.292
PRETERM BIRTH[2]	*25-29*		ref		ref	
	30-34	1.21	0.86 to 1.71	1.06	0.64 to 1.75	
	35-39	0.98	0.68 to 1.43	0.75	0.43 to 1.29	
	40-44	0.94	0.61 to 1.45	0.85	0.47 to 1.54	
	45-49	0.94	0.52 to 1.69	0.83	0.39 to 1.78	
	≥ 50	1.32	0.64 to 2.71	0.57	0.22 to 1.51	
	Per 5 years increase	0.96	0.86 to 1.07	0.91	0.79 to 1.04	0.387

[1]Adjusted for birth year, gestational age, maternal age, the child's sex.
[2]Adjusted for birth year, maternal age, the child's sex.
Abbreviations: IVF- in vitro fertilization, ICSI- intra-cytoplasmic sperm injection, OR- odds ratio, CI- confidence interval, SGA- small for gestational age.

TABLE 7: ASSOCIATION OF PATERNAL AGE WITH ADVERSE NEONATAL OUTCOMES, ACCORDING TO CONCEPTION METHOD. RESTRICTED TO PREGNANCIES WITH MATERNAL AGE BETWEEN 28 AND 41 YEARS, WITH ADJUSTMENT FOR MATERNAL AGE IN TWO- YEAR CATEGORIES.

		TOTAL		SC		All ART combined		
	Paternal age	**OR**	**95 % CI**	**OR**	**95 % CI**	**OR**	**95% CI**	**P interaction**
SGA	*25-29*	1	ref	1	ref	1	ref	
	30-34	0.96	0.93 to 1.00	0.96	0.92 to 1,00	1.25	0.83 to 1.90	
	35-39	1.01	0.97 to 1.06	1.00	0.96 to 1.05	1.28	0.84 to 1.96	
	40-44	1.17	1.11 to 1.23	1.16	1.10 to 1.23	1.34	0.85 to 2.12	
	45-49	1.19	1.10 to 1.28	1.20	1.11 to 1.29	0.96	0.55 to 1.68	
	50-55	1.21	1.07 to 1.36	1.22	1.08 to 1.38	0.99	0.45 to 2.16	
	≥ 55	1.30	1.09 to 1.56	1.35	1.13 to 1.62	0.22	0.03 to 1.70	
	Per 5 years increase	1.05	1.04 to 1.08	1.06	1.04 to 1.07	0.97	0.90 to 1.05	0.09
PRETERM BIRTH	*25-29*	1	ref	1	ref	1	ref	
	30-34	0.91	0.88 to 0.94	0.90	0.87 to 0.94	1.03	0.77 to 1.37	
	35-39	0.93	0.90 to 0.97	0.93	0.89 to 0.96	0.78	0.58 to 1.05	
	40-44	0.96	0.92 to 1.00	0.96	0.91 to 1.00	0.80	0.58 to 1.11	
	45-49	1.05	0.99 to 1.12	1.05	0.99 to 1.12	0.89	0.60 to 1.31	
	50-55	1.07	0.97 to 1.19	1.08	0.97 to 1.20	0.78	0.44 to 1.39	
	≥ 55	1.11	0.95 to 1.30	1.08	0.92 to 1.27	1.43	0.74 to 2.78	
	Per 5 years increase	1.02	1.00 to 1,03	1.02	1.00 to 1.03	0.96	0.90 to 1.04	0.02
PERINATAL DEATH	*25-29*	1	ref	1	ref	1	ref	
	30-34	0.99	0.89 to 1.10	0.98	0.87 to 1.09	2.47	0.57 to 10.68	
	35-39	1.09	0.97 to 1.23	1.09	0.96 to 1.22	1.79	0.39 to 8.18	
	40-44	1.18	1.03 to 1.36	1.17	1.02 to 1.35	2.15	0.45 to 10.21	
	45-49	1.13	0.93 to 1.37	1.14	0.94 to 1.39	1.08	0.17 to 6.84	
	50-55	1.24	0.90 to 1.71	1.25	0.91 to 1.74	1.22	0.11 to 13.67	
	≥ 55	1.05	0.63 to 1.76	1.09	0.65 to 1.83	1	-[2]	
	Per 5 years increase	1.05	1.01 to 1.08	1.05	1.01 to 1.09	0.89	0.72 to 1.11	0.3

[1]Adjusted for birth year, maternal age, parity, the child's sex.
[2]Too few observations.
Abbreviations: SC – spontaneous conception, ART - assisted reproductive technology, OR- odds ratio, CI- confidence interval, SGA- small for gestational age.

TABLE 8: ASSOCIATION OF PATERNAL AGE WITH ADVERSE NEONATAL OUTCOMES, ACCORDING TO ART FERTILIZATION METHOD. RESTRICTED TO PREGNANCIES WITH MATERNAL AGE BETWEEN 28 AND 41 YEARS, WITH ADJUSTMENT FOR MATERNAL AGE IN TWO- YEARS CATEGORIES.

		IVF		ICSI		
	Paternal age	**OR[2]**	**95% CI[2]**	**OR[2]**	**95% CI[2]**	**P interaction**
SGA	*25-29*	1	ref	1	ref	
	30-34	1.07	0.67 to 1.72	1.94	0.70 to 5.39	
	35-39	1.01	0.63 to 1.63	2.67	0.96 to 7.46	
	40-44	0.99	0.58 to 1.67	3.14	1.09 to 9.05	
	45-49	0.62	0.30 to 1.27	2.57	0.81 to 8.11	
	≥ 50	0.79	0.31 to 2.04	0.94	0.20 to 4.30	
	Per 5 years increase	0.94	0.84 to 1.05	1.05	0.93 to 1.19	0.2
PRETERM BIRTH	*25-29*		ref		ref	
	30-34	1.03	0.73 to 1.46	1.08	0.60 to 1.93	
	35-39	0.87	0.61 to 1.24	0.69	0.38 to 1.27	
	40-44	0.91	0.61 to 1.34	0.76	0.40 to 1.45	
	45-49	0.97	0.59 to 1.59	0.92	0.45 to 1.88	
	≥ 50	1.55	0.84 to 2.85	0.51	0.20 to 1.27	
	Per 5 years increase	1.03	0.93 to 1.13	0.91	0.80 to 1.03	0.90

[1]Adjusted for birth year, maternal age, parity, the child's sex.
Abbreviations: IVF- in vitro fertilization, ICSI- intra-cytoplasmic sperm injection, OR- odds ratio, CI- confidence interval, SGA- small for gestational age.

TABLE 9: ASSOCIATION OF PATERNAL AGE WITH BIRTH WEIGHT AND GESTATIONAL AGE, ACCORDING TO CONCEPTION METHOD.

		TOTAL		SC		All ART combined		
	Paternal age	**Mean difference**	**(95% CI)**	**Mean difference**	**(95% CI)**	**Mean difference**	**(95% CI)**	**P interaction**
BIRTH WEIGHT[1]	*25-29*	ref	-	ref	-	ref	-	
	30-34	-3.4	-5.8 to -1.1	-3.3	-5.7 to -0.9	-11.9	-43.8 to 20.0	
	35-39	-11.5	-14.5 to -8.4	-11.5	-14.6 to -8.4	-3.1	-37.4 to 31.2	
	40-44	-26.4	-30.6 to -22.1	-26.4	-30.7 to -22.1	-14.2	-51.9 to 23.5	
	45-49	-35.5	-42.1 to -28.9	-36.8	-43.5 to -30.2	28.5	-19.3 to 76.4	
	50-55	-35.1	-46.5 to -23.7	-37.0	-48.6 to -25.4	40.8	-27.6 to 109.2	
	≥ 55	-43.5	-61.7 to -25.4	-45.9	-64.4 to -27.3	42.0	-41.3 to 125.4	
	Per 5 years increase	-8.9	-10.0 to -7.7	-9.0	-10.2 to -7.8	4.2	-4.2 to 12.7	0.1
GESTATIONAL AGE[2]	*25-29*	ref	-	ref	-	ref	-	
	30-34	0.1	0.0 to 0.2	0.1	0.0 to 0.2	-0.1	-1.3 to 1.0	
	35-39	0.1	-0.0 to 0.2	0.1	-0.0 to 0.2	1.2	-0.1 to 2.4	
	40-44	-0.2	-0.3 to -0.1	-0.2	-0.4 to -0.1	1.4	0.1 to 2.8	
	45-49	-0.6	-0.8 to -0.4	-0.6	-0.8 to -0.4	0.5	-1.3 to 2.2	
	50-55	-0.7	-1.1 to -0.4	-0.8	-1.1 to -0.4	0.9	-1.6 to 3.3	
	≥ 55	-0.9	-1.5 to -0.4	-0.9	-1.5 to -0.4	-0.4	-3.6 to 2.9	
	Per 5 years increase	-0.1	-0.1 to -0.1	-0.1	-0.1 to -0.1	0.3	0.0 to 0.6	<0.001

[1]Adjusted for birth year, gestational age maternal age, parity, the child's sex.
[2]Adjusted for birth year, maternal age, parity, the child's sex.
Abbreviations: SC – spontaneous conception, ART - assisted reproductive technology, CI- confidence interval.

TABLE 10: ASSOCIATION OF PATERNAL AGE WITH BIRTH WEIGHT AND GESTATIONAL AGE, ACCORDING TO ART FERTILIZATION METHOD

		IVF		ICSI		
	Paternal age	**Mean difference**	**(95% CI)**	**Mean difference**	**(95% CI)**	**P interaction**
BIRTH WEIGHT[1]	*25-29*	ref	-	ref	-	
	30-34	-11.9	-52.6 to 28.8	-25.0	-80.7 to 30.7	
	35-39	2.8	-40.8 to 46.4	-31.7	-91.3 to 28.0	
	40-44	-0.2	-48.9 to 48.6	-58.3	-122.7 to 6.0	
	45-49	40.7	-20.0 to 101.4	-6.5	-90.4 to 77.3	
	≥ 50	37.3	-40.7 to 115.2	26.2	-66.4 to 118.9	
	Per 5 years increase	6.8	-4.3 to 17.9	-1.7	-15.7 to 12.3	0.64
GESTATIONAL AGE[2]	*25-29*	ref	-	ref	-	
	30-34	0.0	-1.5 to 1.6	0.1	-1.8 to 2.0	
	35-39	1.2	-0.4 to 2.8	1.3	-0.7 to 3.3	
	40-44	1.3	-0.5 to 3.2	1.2	-1.1 to 3.4	
	45-49	0.4	-1.9 to 2.8	0.4	-2.3 to 3.1	
	≥ 50	-0.7	-4.0 to 2.7	1.2	-1.8 to 4.2	
	Per 5 years increase	0.3	-0.2 to 0.7	0.3	-0.2 to 0.7	0.36

[1]Adjusted for birth year, gestational age maternal age, parity, the child's sex.
[2]Adjusted for birth year, maternal age, parity, the child's sex.
Abbreviations: IVF- in vitro fertilization, ICSI- intra-cytoplasmic sperm injection, CI- confidence interval.

TABLE 11: ASSOCIATION OF PATERNAL AGE WITH BIRTH WEIGHT AND GESTATIONAL AGE, ACCORDING TO CONCEPTION METHOD. RESTRICTED TO PREGNANCIES IN NULLIPAROUS WOMEN.

		TOTAL		SC		All ART combined		
	Paternal age	**Mean difference**	**(95% CI)**	**Mean difference**	**(95% CI)**	**Mean difference**	**(95% CI)**	**P interaction**
BIRTH WEIGHT	*25-29*	ref	-	ref	-	ref	-	
	30-34	-11.0	-14.3 to -7.7	-10.8	-14.1 to -7.4	-17.0	-53.1 to 19.2	
	35-39	-21.9	-26.4 to -17.4	-22.3	-26.9 to -17.8	-10.5	-49.3 to 28.4	
	40-44	-34.1	-40.9 to -27.3	-34.4	-41.3 to -27.5	-25.2	-68.7 to 18.3	
	45-49	-30.8	-41.5 to -20.1	-33.7	-44.7 to -22.7	25.4	-31.9 to 82.8	
	50-55	-23.3	-40.7 to -5.9	-27.0	-44.9 to -9.1	39.2	-40.2 to 118.6	
	≥ 55	-37.6	-65.1 to -10.0	-42.8	-71.3 to -14.4	55.3	-51.3 to 161.9	
	Per 5 years increase	-9,8	-11.3 to -8.3	-10.2	-11.8 to -8.6	3.9	-6.0 to 13.7	0.003
GESTATIONAL AGE	*25-29*	ref	-	ref	-	ref	-	
	30-34	0.0	-0.1 to 0.1	0.0	-0.1 to 0.1	-0.6	-1.9 to 0.7	
	35-39	-0.1	-0.2 to 0.1	-0.1	-0.2 to 0.1	0.8	-0.6 to 2.2	
	40-44	-0.2	-0.4 to 0.0	-0.2	-0.5 to 0.0	1.0	-0.6 to 2.7	
	45-49	-0.5	-0.9 to -0.1	-0.5	-0.9 to -0.2	1.1	-0.9 to 3.1	
	50-55	-0.8	-1.5 to -0.2	-0.8	-1.5 to -0.2	0.1	-2.8 to 3.0	
	≥ 55	-1.1	-2.0 to -0.2	-1.0	-1.9 to -0.1	-1.9	-6.3 to 2.5	
	Per 5 years increase	-0.1	-0.1 to 0.0	-0.1	-0.2 to 0.0	0.4	0.1 to 0.8	<0.001

[1]Adjusted for birth year, maternal age, the child's sex.
Abbreviations: SC – spontaneous conception, ART - assisted reproductive technology, CI- confidence interval

TABLE 12: ASSOCIATION OF PATERNAL AGE WITH BIRTH WEIGHT AND GESTATIONAL AGE, ACCORDING TO ART FERTILIZATION METHOD. RESTRICTED TO PREGNANCIES IN NULLIPAROUS WOMEN.

		IVF		ICSI		
	Paternal age	**Mean difference**	**(95% CI)**	**Mean difference**	**(95% CI)**	**P interaction**
BIRTH WEIGHT[1]	*25-29*	ref	-	ref	-	
	30-34	-20.4	-67.0 to 26.3	-26.0	-87.8 to 35.8	
	35-39	-7.8	-57.7 to 42.1	-22.5	-89.6 to 44.6	
	40-44	-22.6	-79.4 to 34.1	-41.2	-115.5 to 33.0	
	45-49	27.7	-46.1 to 101.5	22.9	-77.3 to 123.0	
	≥ 50	31.4	-60.6 to 123.3	55.6	-55.9 to 167.1	
	Per 5 years increase	3.3	-9.6 to 16.1	5.4	-11.4 to 22.1	0.806
GESTATIONAL AGE[2]	*25-29*	ref	ref	ref	ref	
	30-34	-0.4	-2.2 to 1.4	-0.5	-2.6 to 1.7	
	35-39	0.9	-0.9 to 2.7	0.9	-1.5 to 3.2	
	40-44	0.7	-1.5 to 2.9	1.2	-1.5 to 3.8	
	45-49	1.4	-1.4 to 4.2	0.6	-2.5 to 3.8	
	≥ 50	-0.5	-4.2 to 3.2	-0.6	-4.5 to 3.4	
	Per 5 years increase	0.4	-0.1 to 0.9	0.2	-0.3 to 0.8	0.199

[1]Adjusted for birth year, gestational age, maternal age, the child's sex.
[2]Adjusted for birth year, maternal age, the child's sex.
Abbreviations: IVF- in vitro fertilization, ICSI- intra-cytoplasmic sperm injection, CI- confidence interval.

TABLE 13: ASSOCIATION OF PATERNAL AGE WITH BIRTH WEIGHT AND GESTATIONAL AGE, ACCORDING TO CONCEPTION METHOD. RESTRICTED TO PREGNANCIES WITH MATERNAL AGE BETWEEN 28 AND 41 YEARS, WITH ADJUSTMENT FOR MATERNAL AGE IN TWO- YEARS CATEGORIES.

		TOTAL		SC		All ART combined		
	Paternal age	**Mean difference**	**(95% CI[2])**	**Mean difference**	**(95% CI[2])**	**Mean difference**	**(95% CI[2])**	**P interaction**
BIRTH WEIGHT[1]	*25-29*	ref	-	ref	-	ref	-	
	30-34	4.1	0.7 to 7.6	4.4	0.9 to 7.8	-24.5	-63.4 to 14.4	
	35-39	-2.9	-7.0 to 1.1	-2.9	-7.0 to 1.1	-11.0	-51.8 to 29.7	
	40-44	-17.5	-22.6 to 12.5	-17.6	-22.7 to -12.5	-20.5	-64.4 to 23.5	
	45-49	-27.3	-34.7 to -19.9	-28.9	-36.4 to -21.4	27.3	-26.7 to 81.2	
	50-55	-27.7	-40.4 to -15.0	-30.0	-42.9 to -17.0	37.8	-37.3 to 112.8	
	≥ 55	-36.1	-56.1 to -16.0	-38.3	-58.9 to -17.7	23.9	-64.6 to 112.3	
	Per 5 years increase	-7.7	-9.1 to -6.3	-7,9	-9,3 to -6,5	8,7	-3.2 to 20.5	0.2
GESTATIONAL AGE[2]	*25-29*	ref	-	ref	-	ref	-	
	30-34	0.0	0.0 to 0.0	0.0	0.0 to 0.0	0.1	-0.1 to 0.2	
	35-39	0.0	0.0 to 0.0	-0.0	0.0 to 0.0	0.1	-0.1 to 0.2	
	40-44	0.0	0.0 to 0.0	0.0	0.0 to 0.0	0.0	-0.2 to 0.2	
	45-49	0.0	-0.0 to 0.0	0.0	0.0 to 0.1	0.0	-0.3 to 0.2	
	50-55	0.0	-0.1 to 0.0	0.0	-0.1 to 0.0	0.2	-0.2 to 0.5	
	≥ 55	0.0	-0.1 to 0.1	0.0	-0.1 to 0.1	0.0	-0.5 to 0.4	
	Per 5 years increase	0.0	0.0 to 0.0	0.0	0.0 to 0.0	0.0	-0.1 to 0.0	0.2

[1]Adjusted for birth year, gestational age, parity, the child's sex.
[2]Adjusted for birth year, parity, the child's sex.
Abbreviations: SC – spontaneous conception, ART - assisted reproductive technology, CI- confidence interval

TABLE 14: ASSOCIATION OF PATERNAL AGE WITH BIRTH WEIGHT AND GESTATIONAL AGE, ACCORDING TO ART FERTILIZATION METHOD. RESTRICTED TO PREGNANCIES WITH MATERNAL AGE BETWEEN 28 AND 41 YEARS, WITH ADJUSTMENT FOR MATERNAL AGE IN TWO- YEARS CATEGORIES.

		IVF		ICSI		
	Paternal age	**Mean difference**	**(95% CI)**	**Mean difference**	**(95% CI)**	**P interaction**
BIRTH WEIGHT[1]	*25-29*	ref	ref	ref	ref	
	30-34	-14.0	-60.5 to 32.6	-65.8	-138.9 to 7.4	
	35-39	3.4	-45.2 to 52.0	-66.6	-142.0 to 8.8	
	40-44	1.4	-52.6 to 55.5	-92.0	-172.3 to -11.7	
	45-49	45.9	-20.5 to 112.3	-45.7	-144.1 to 52.8	
	≥ 50	40.9	-43.1 to 124.8	-7.9	-114.7 to 99.0	
	Per 5 years increase	8,7	-3.2 to 20.5	-1.6	-16.9 to 13.6	0.7
GESTATIONAL AGE[2]	*25-29*	ref	ref	ref	ref	
	30-34	0.0	-0.2 to 0.2	0.1	-0.2 to 0.4	
	35-39	-0.1	-0.3 to 0.1	0.3	-0.0 to 0.6	
	40-44	0.0	-0.2 to 0.3	0.1	-0.2 to 0.4	
	45-49	-0.2	-0.5 to 0.1	0.2	-0.2 to 0.6	
	≥ 50	0.0	-0.4 to 0.4	0.1	-0.3 to 0.6	
	Per 5 years increase	-0.0	-0.1 to 0.0	0.0	-0.1 to 0.1	0.6

[1]Adjusted for birth year, gestational age, parity, the child's sex.
[2]Adjusted for birth year, parity, the child's sex.
Abbreviations: IVF- in vitro fertilization, ICSI- intra-cytoplasmic sperm injection, CI- confidence interval.