

ADVANCED PATERNAL AGE AND PARTNERED INTRAUTERINE INSEMINATION OUTCOMES

Ralica Petkova^{1✉}, Desislava Dyulgerova-Nikolova^{1,2},
Tanya Milachich^{1,2}, Maria Yunakova^{1,3}

Received on February 3, 2026

Presented by B. Petrunov, Member of BAS, on May 26, 2026

Abstract

The aim of this study was to evaluate the association between advanced paternal age (APA) and intrauterine insemination (IUI) outcomes. This retrospective cohort study included 861 IUI cycles in couples in which the female partner was ≤ 35 years. Patients were stratified according to paternal age into a control group (< 40 years) and a study group (≥ 40 years). The study group was further subdivided into two categories of APA: men aged 40–44 years and ≥ 45 years. Primary outcomes were clinical pregnancy rate (CPR), miscarriage rate (MR), and live-birth rate (LBR).

No significant differences were observed between the control and the study groups in CPR (17.9% vs. 16.9%), MR (7.5% vs. 15.7%), or LBR (15.2% vs. 12.8%) (all $p > 0.05$). A subgroup analysis showed no differences between controls and men aged 40–44 years. In contrast, in men aged ≥ 45 years, MR was significantly higher (44.4% vs. 7.5%, $p < 0.05$) and LBR was significantly lower (6.6% vs. 15.2%, $p < 0.05$). Paternal age of 45 years or older is associated with increased miscarriage rates and reduced live-birth rates following IUI, whereas no effect was observed for the 40–44 age group.

Key words: advanced paternal age, intrauterine insemination, pregnancy rate, miscarriage rate

Introduction. Over recent years, the average age of first-time fathers has steadily increased, particularly in Europe, where an approximate 4.5-year rise has

been reported over the past two decades [1]. This trend is attributed to delayed family formation, increased life expectancy, and socio-economic factors. Assisted reproduction technology (ART) has progressed significantly in response to lifestyle changes and reproductive behaviour. It is widely established that maternal age is one of the most important factors influencing the success of ART. After the age of 40, the success rate of ART declines sharply due to reduced oocyte quantity as well as quality, and impaired implantation. In contrast, the role of paternal age remains less clearly defined.

Advanced paternal age (APA), typically defined as 40 years or older, has been linked to adverse reproductive outcomes, including impaired sperm quality, increased DNA fragmentation, and chromosomal abnormalities. A study published in 2018 examined the impact of paternal factors on a wide spectrum of perinatal and pediatric outcomes [2]. Current evidence indicates that APA is associated with sperm-DNA strand breaks and chromosomal anomalies – both related to increased risk of pregnancy loss [3].

In the context of ART, particularly intrauterine insemination (IUI), the literature presents conflicting evidence regarding the influence of paternal age on pregnancy outcomes. Several studies have found no significant association between paternal age and ART outcomes [4]. TATSUMI et al. [5] reported that the advanced age of the male partner, in isolation, does not negatively affect pregnancy or live-birth rates following IUI. In contrast, other researchers have observed reduced pregnancy and live-birth rates among couples where the male partner is 45 years or older compared to younger men [6]. Currently, there is no universally accepted threshold for defining APA in the context of IUI. However, a review of the literature indicates that infertility and reproductive risks increase substantially after the age of 40, which is frequently used as the clinical cutoff for APA [7].

The present study aimed to evaluate the effect of paternal age on IUI outcomes in a cohort with controlled female age.

Materials and methods. A retrospective cohort study was conducted including 861 couples undergoing their first IUI cycle at the Ob/Gyn Hospital Dr. Shterev between January 2020 and September 2023.

Inclusion criteria:

- Female age 18–35 years
- Male age 20–53 years
- Sperm concentration $\geq 20 \times 10^6/\text{mL}$,
- Progressive motility (a + b) $\geq 25\%$
- Normal morphology $\geq 4\%$

Exclusion criteria:

- Female age > 35 years
- Severe male factor infertility
- Incomplete outcome data ($n = 12$ excluded)

To ensure independence of observations, only the first intrauterine insemination (IUI) cycle per couple was included. Couples were divided into two groups based on paternal age at the time of IUI: men younger than 40 years (control group) and men aged 40 years or older (study group). The primary outcomes were clinical pregnancy rate (CPR), defined as ultrasound-confirmed gestation; miscarriage rate (MR), defined as pregnancy loss after confirmed gestation; live-birth rate (LBR), defined as live birth per initiated cycle. The study group was further subdivided into two APA categories: men aged 40–44 years and those aged 45 years or older. CPR, LBR, and MR were also observed in these subgroups and compared with the control group.

Induction of ovulation. Only cycles involving controlled ovulation induction were included. The number of developing follicles was one or two. If three or more follicles were visualized, the IUI procedure was cancelled due to an increased risk of multiple pregnancy.

Analysis and sperm sample preparation for IUI. After 2–5 days of sexual abstinence, semen samples were obtained by masturbation into a sterile container. Semen analysis was performed in accordance with World Health Organization (WHO, 5th edition) guidelines. Sperm morphology was assessed using Kruger's strict criteria. Sperm processing was performed using density gradient centrifugation (DGC) (SpermGrad™; Vitrolife). According to the laboratory protocol, IUI was cancelled if the post-wash total motile sperm count (TMSC) was $< 10 \times 10^6/\text{mL}$.

Statistical analysis. The statistical analysis was performed using the Student's *t*-test. Results with $p \leq 0.05$ were considered statistically significant.

Results. A total of 861 couples who met the inclusion criteria were analyzed retrospectively. The age of the female partners did not differ significantly between the control and study groups (24.3 ± 1.5 years vs. 25.6 ± 1.1 years, $p > 0.05$) (Table 1). The mean age of the male partner was 34.7 ± 2.8 years in the control group and 42.3 ± 2.7 years in the study group ($p > 0.05$) (Table 1). All couples underwent IUI. After DGC, post-wash TMSC was at least $10 \times 10^6/\text{mL}$. The number of IUI procedures was similar across groups (446 vs. 415). CPR did not differ significantly between the control and study groups (17.9% vs. 16.9%, $p > 0.05$) (Table 1). MR was 7.5% in the control group and 15.7% in the study group ($p > 0.05$), but this difference was not statistically significant (Table 1). Furthermore, LBR also showed no significant variation between the paternal age groups (15.2% vs. 12.8%, $p > 0.05$) (Table 1).

Primary outcomes were analyzed across two APA categories: men aged 40–44 years and those aged 45 years or older, compared to the control group. The number of IUI procedures in these subgroups were 279 and 136, respectively (Tables 2, 3). Comparison between the control group and the 40–44 years subgroup showed no statistically significant differences in CPR (17.9% vs. 18.6%, $p > 0.05$), MR (7.5% vs. 5.8%, $p > 0.05$), or LBR (15.2% vs. 15.8%, $p > 0.05$) (Table 2).

T a b l e 1

Mean age and clinical outcomes in the control and study groups

Parameter	Control group <i>n</i> = 446	Study group <i>n</i> = 415	<i>p</i> -value
Female age (years)	24.3±1.5	25.6 ± 1.1	<i>p</i> > 0.05
Male age (years)	34.7± 2.8	42.3 ± 2.7	<i>p</i> > 0.05
CPR (%)	17.9	16.9	<i>p</i> > 0.05
MR (%)	7.5	15.7	<i>p</i> > 0.05
LBR (%)	15.2	12.8	<i>p</i> > 0.05

CPR, clinical pregnancy rate; MR, miscarriage rate; LBR, live-birth rate. *p*-values for all factors were assessed using Student's *t*-test.

T a b l e 2

Clinical outcomes in the control and the 40–44 years groups

Outcome	Control group <i>n</i> = 446	40–44 years <i>n</i> = 279	<i>p</i> -value
CPR (%)	17.9	18.6	<i>p</i> > 0.05
MR (%)	7.5	5.8	<i>p</i> > 0.05
LBR (%)	15.2	15.8	<i>p</i> > 0.05

CPR, clinical pregnancy rate; MR, miscarriage rate; LBR, live-birth rate. *p*-values for all factors were assessed using Student's *t*-test.

Within the ≥ 45 years subgroup, CPR was lower compared with the control group but did not differ significantly (13.2% vs. 17.9%, *p* > 0.05) (Table 3). In contrast, MR was significantly higher in this subgroup compared to the control group (44.4% vs. 7.5%, *p* < 0.05), while LBR was significantly lower (6.6% vs. 15.2%, *p* < 0.05) (Table 3).

T a b l e 3

Clinical outcomes in the control and ≥ 45 years groups

Outcome	Control group <i>n</i> = 446	≥ 45 years <i>n</i> = 136	<i>p</i> -value
CPR (%)	17.9	13.2	<i>p</i> > 0.05
MR (%)	7.5	44.4	<i>p</i> < 0.05*
LBR (%)	15.2	6.6	<i>p</i> < 0.05*

CPR, clinical pregnancy rate; MR, miscarriage rate; LBR, live-birth rate. *p*-values for all factors were assessed using Student's *t*-test. *Statistically significant.

Discussion. The present study evaluated the impact of APA on IUI outcomes in a cohort with controlled female age. Our findings demonstrate no significant differences in CPR, MR, or LBR between men aged 40–44 years and the control group of younger men. However, significantly poorer outcomes were observed in the subgroup aged 45 years and older, particularly regarding miscarriage and live-birth rates.

The absence of a significant effect of paternal age in the 40–44 years group aligns with previous studies suggesting that moderate increases in paternal age do not independently impair reproductive outcomes following IUI. Tatsumi et al. [5] reported no adverse effect of APA on clinical pregnancy or LBR after IUI, indicating that paternal age alone may not be a decisive determinant of success in IUI cycles. Similarly, other retrospective analyses have demonstrated that female age remains the dominant predictor of IUI outcomes, while paternal age has limited independent impact within certain thresholds [8].

In contrast, evidence from broader ART populations indicates a potential detrimental effect of increasing paternal age, particularly beyond 45–50 years. A recent meta-analysis of over 32 000 ART cycles reported lower LBR and higher MR with increasing paternal age, even after controlling for maternal age in donor oocyte cycles [9]. These findings support the possibility that the impact of paternal age may become more pronounced beyond a specific biological threshold. Additional studies have reported a correlation between increased paternal age and higher miscarriage rates among patients undergoing artificial insemination. For example, a study conducted in France reported a higher incidence of spontaneous abortions following IUI in couples with older male partners (≥ 45 years): 32.4%, compared to 13.7% when the male was under 30 years [10]. The significantly higher MR and reduced LBR observed in the ≥ 45 years subgroup in the present study are consistent with these observations. The biological plausibility of these findings is supported by evidence demonstrating age-related deterioration in sperm DNA integrity, including increased DNA fragmentation and chromosomal abnormalities, both of which have been associated with higher miscarriage risk [11].

Systematic reviews of IUI indicate that overall LBR per cycle remains relatively low, particularly among women of advanced reproductive age [12]. However, evidence specifically addressing the impact of paternal age on IUI outcomes is limited and heterogeneous. Furthermore, there is no universally accepted age threshold that defines “advanced paternal age” in the context of IUI outcomes.

Taken together, our findings suggest that while moderate paternal age (40–44 years) may not significantly influence IUI outcomes, advanced age ≥ 45 years may be associated with poorer reproductive outcomes.

Conclusion. Paternal age between 40 and 44 years does not appear to be associated with adverse IUI outcomes. However, a paternal age of 45 years or older is linked to higher miscarriage rates and lower live-birth rates. These results

suggest the existence of a potential age threshold effect for advanced paternal age (APA), particularly concerning pregnancy loss and live birth. Additional prospective studies are necessary to validate these findings and to establish clinically relevant paternal age cutoffs for IUI.

REFERENCES

- [1] PAAVILAINEN M., A. BLOIGU, E. HEMMINKI et al. (2016) Aging fatherhood in Finland – first-time fathers in Finland from 1987 to 2009, *Scand. J. Public Health*, **44**(4), 423–430.
- [2] OLDEREID N. B., U. B. WENNERHOLM, A. PINBORG et al. (2018) The effect of paternal factors on perinatal and paediatric outcomes: a systematic review and meta-analysis, *Hum. Reprod. Update*, **24**(3), 320–389.
- [3] ROBINSON L., I. D. GALLOS, S. J. CONNER et al. (2012) The effect of sperm DNA fragmentation on miscarriage rates: a systematic review and meta-analysis, *Hum. Reprod.*, **27**(10), 2908–2917.
- [4] WHITCOMB B. W., R. TURZANSKI-FORTNER, K. S. RICHTER et al. (2011) Contribution of male age to outcomes in assisted reproductive technologies, *Fertil. Steril.*, **95**(1), 147–151.
- [5] TATSUMI T., E. ISHIDA, K. TATSUMI et al. (2018) Advanced paternal age alone does not adversely affect pregnancy or live-birth rates or sperm parameters following intrauterine insemination, *Reprod. Med. Biol.*, **17**(4), 459–465.
- [6] FARABET C., P. PIRTEA, A. BENAMMAR et al. (2024) The impact of paternal age on cumulative assisted reproductive technology outcomes, *Front. Med.*, **10**, 1294242.
- [7] NYBO ANDERSEN A. M., K. D. HANSEN, P. K. ANDERSEN (2004) Advanced paternal age and risk of fetal death: a cohort study, *Am. J. Epidemiol.*, **160**(12), 1214–1222.
- [8] STAROSTA A., C. E. GORDON, M. D. HORNSTEIN (2020) Predictive factors for intrauterine insemination outcomes: a review, *Fertil. Res. Pract.*, **6**(1), 23.
- [9] MURUGESU S., L. S. KASAVEN, A. PETRIE et al. (2022) Does advanced paternal age affect outcomes following assisted reproductive technology? A systematic review and meta-analysis, *Reprod. Biomed. Online*, **45**(2), 283–331.
- [10] KALTSAS A., A. ZIKOPOULOS, D. VRACHNIS et al. (2024) Advanced paternal age in focus: unraveling its influence on assisted reproductive technology outcomes, *J. Clin. Med.*, **13**(10), 2731.
- [11] GONZALEZ D. C., J. ORY, R. BLACHMAN-BRAUN et al. (2022) Advanced paternal age and sperm DNA fragmentation: a systematic review, *World J. Mens Health*, **40**(1), 104–115.
- [12] NESBIT C. B., M. BLANCHETTE-PORTER, N. ESFANDIARI (2022) Ovulation induction and intrauterine insemination in women of advanced reproductive age: a systematic review of the literature, *J. Assist. Reprod. Genet.*, **39**(7), 1445–1491.

¹*IVF Department, Ob/Gyn Hospital “Dr. Shterev”, 25–31 Hristo Blagoev St,
1330 Sofia, Bulgaria
e-mails: petkovaralica@abv.bg, dess_ie@mail.bg, tanya_ivf@yahoo.com,
m_yunakova@yahoo.com*

²*Institute of Biology and Immunology of Reproduction, Bulgarian Academy of Sciences,
73 Tsarigradsko Shosse Blvd, 1113 Sofia, Bulgaria*

³*Department of Obstetrics and Gynecology, Medical University - Sofia,
2 Zdrave St, 1431 Sofia, Bulgaria*