The Impact of Paternal Age on Cumulative Assisted Reproductive Technologies Outcomes

Clemence Farabet  
Hospital FOCH

Paul Pirtea (✉ paulpirtea@gmail.com)  
Hospital FOCH

Achraf Benammar PhrD  
Hospital FOCH

Dominique Ziegler  
Hospital FOCH

Claire Marchiori  
Hospital FOCH

Alexandre Vallée  
Hospital FOCH

Jean-Marc Ayoubi  
Hospital FOCH

Research Article

Keywords: Paternal age, ART, fresh embryo transfer, frozen embryo transfer

Posted Date: April 12th, 2023

DOI: https://doi.org/10.21203/rs.3.rs-2786449/v1

License: ☺️  This work is licensed under a Creative Commons Attribution 4.0 International License. 
Read Full License
Abstract

Objective: To investigate the impact of paternal age on cumulative live birth rate in ART

Design: Retrospective single center cohort study

Patient(s): All female patients 18-43 years old, and males 18-60 years old who performed their first ART cycle between January 2018 and December 2020 were included.

Intervention(s): N/A

Main Outcome Measure(s): The primary outcome, cumulative live birth rate (cLBR), was estimated following fresh or frozen embryo transfers issued from an ART cycle. Secondary outcomes included: cumulative pregnancy rate (cPR), miscarriage rate. subgroups analyses were performed, as follows: males <45 and ≥ 45; female <35,35-38, and >38 years.

Result(s): 2,358 couples were included. Male patients within both age groups had sperm quantity divided in 2 groups: normal and abnormal, that were found to be in significantly equal proportions. There was significantly more tobacco use in the male group ≥45. cPR was 0.5301 in the group <45 and 0.3111 in the group ≥45, p < 0.001. Analysis according to the female age, in the female group > 38: cLBR rate was 0.26 for male <45 and 0.19 for male ≥45, p=0.061. Also, cPR was 0.34 in the male group <45 and 0.21 in the group ≥45, p< 0.001. In the female group 35-38 cLBR was 0.44 in the male group <45 and 0.3 in the group ≥45, p=0.031. cPR was 0.49 in the male group <45 and 0.34 in the group ≥ 45, p=0.036. Within the female group <35, we observed non-significant results. Miscarriage rate results weren't significantly different for women ≤38.

Conclusion: According to our result, male age ≥45 has a significant impact on cumulative ART outcomes.

Impact statement: We report that male age ≥45 has a significant impact on cumulative ART outcomes, an effect particularly pronounced in women over 38 years of age.

Introduction

In Assisted Reproductive Technologies (ART), women's age has long been recognized as the most predictive factor. This effect parallels the fact that maternal age is strongly associated with couples’ chances of natural conception. In ART, increasing maternal age – notably, beyond 35 years – is associated with increased risk of embryo aneuploidy, implantation failure and miscarriage (1). Conversely, the age of the male partner has received lesser interest. Demonstrating a relationship between paternal age and poor ART outcomes is a challenging task due to the inherent difficulty at singling out the father’s age from the maternal one or other confounders. Some studies reported a positive relationship between increased paternal age and poor ART outcomes (2–5), but no clearly defined age threshold has been validated. Some authors reported a lower pregnancy (PR) and livebirth rate (LBR) after controlling for maternal age and other confounders for male over 46 years old (6) or over 50 years old (7), compared
to younger male. In contrast however, when restricted to women aged < 35 years there was no significant difference between the two male groups (6).

Mc Pherson et al. reported a decrease in LBR among couples whose female partner was > 35 years and the male partner > 40 years of age. They hypothesized that the negative effect stemmed from an increase in sperm DNA fragmentation, alteration of oocyte’s cytoplasm DNA repair mechanisms in these couples (8).

Poorer spermatic parameters as well as changes in the genetic and epigenetic status of spermatozoa in ageing males have been found as possible causative factor in the overall decline in ART outcome (3, 9–12). The known effects of paternal age on reproduction include an alteration of sperm parameters and genomic alteration characterized by spontaneous mutations, sperm DNA fragmentation and telomere shortening (13).

In contrast, other studies have found no significant impact of paternal age on ART results (9, 14, 15). In a study involving 278 couples, Nijs et al. observed no difference in fertilization rates, pregnancy rates, and LBRs related to paternal age when controlling for maternal age (16). Yet, these authors excluded, men with severe oligo-astheno-teratozoospermia (OAT), those who used testicular sperm for ICSI, and cases involving preimplantation genetic testing while this represents a significant portion of the patients managed in IVF (16).

As women seeking ART are progressively older, the role of male age gains more interest.

Nowadays, the average age of conception for a couple is continuously increasing year after year. Regarding paternal age, according to a 2017 review, fathers at the time of their first child's birth are on average 3.5 years older than 40 years ago (17). Over the same period, the percentage of fathers over 49 years old has doubled (17).

This discrepancy between reports of poorer ART outcome when the male partner is older and the observation of constant – age independent – donor egg ART results has led us to question whether male age might have a more important effect in older women. In donor egg ART oocyte donors are generally young and this may negate any impact of male’s age.

Indeed, success rates of donor egg ART remain constant until the age of fifty years even though in general the male partner is slightly older than his spouse (2–4) This has greatly contributed to believe that the role of the age of the male partner is of menial importance if any in ART.

To test this hypothesis, we elected to study the impact of male age on ART outcomes as a function of the female’s age. We therefore decided to analyze the possible impact of paternal age on cumulative ART outcome in different age categories of men and women.

**Material And Methods**
We conducted a retrospective cohort study including all IVF or ICSI cycles performed at Foch hospital from January 2016 to December 2020. We included all women from 18 - 43 years and male from 18 years to 59 years, who underwent their first ART cycle at Foch hospital. We excluded those couples where sperm was obtained from a testicular biopsy or a donor and those with a number of oocytes retrieved strictly inferior to 4. We characterized male by sperm parameters and the use of tobacco. We collected AMH levels and total dose of gonadotropin used in controlled ovarian stimulation (COS). Biochemical pregnancies were excluded. At each embryo transfer, the embryo with the best morphology as determined by Gardner scale, were transferred first. Cumulative results for pregnancy rate (PR) and live birth rate (LBR) were calculated after all embryos were transferred or until the obtention of the first live birth. The main outcome was cumulative live birth rate (cLBR) and the secondary outcomes were cumulative pregnancy rate (cPR) defined by the presence of cardiac activity at the time of the first ultrasound approximatively 7-8 weeks after the embryo transfer. Also, the miscarriage rate was assessed, defined as any pregnancy in which cardiac activity stopped before 12 weeks of gestation.

ETHICAL APPROVAL

Given the retrospective nature of this study, the access and processing of patient data was approved by the CERF – French Research Ethic Committee IRB 00012437 from 13/04/2022.

PATIENT TREATMENT

The ART treatment followed FOCH AMP routine protocols. COS was performed using highly purified urinary menotropins (hMG) and recombinant FSH (rFSH). For OS, individually set doses of hMG and/or rFSH were used, ranging from 150–600 IU/day in an GnRH-antagonist protocol. Development of ovarian follicles was monitored by transvaginal ultrasonography beginning on the seventh day of OS. If required, hormonal doses were adjusted to generate an optimal ovarian response. The gonadotropin-releasing hormone (GnRH) antagonist (Cetrorelix® 0.25 mg Merck France) was introduced systematically on the sixth day of OS.

Final oocyte maturation was triggered using a combination of human chorionic gonadotropin (hCG) (Ovitrelle® 250 µg Merck France)with 2 ampules of GnRH agonist, triptoreline Decaptyl® (0.1 mg Ipsen France), or triptoreline only GnRH 0.3mg, if there was a risk of an ovarian hyperstimulation syndrome, when ≥3 mature follicles of ≥18 mm were confirmed by vaginal ultrasound. Transvaginal oocyte retrieval (TVOR) was performed 36 hours after ovulation trigger. The thickness of the endometrium had to be greater than 7mm, and progesterone less than 1.5 ng/ml on the day of the ovulation trigger, to perform a fresh embryo transfer. If there was a risk of hyperstimulation, or an incidental discovery of polyps, the entire cohort of embryos were frozen. Mature oocytes were fertilized by using ICSI if considered necessary. Blastocyst embryos were graded according. Embryos were cultured in 90% N₂, 5% O₂ and 5% CO₂ mixture at 37 ºC. Blastocysts were analyzed on day 5 and/or 6 and graded. Excellent and good-quality embryos were defined as B3-B4 or B5 embryos ≥4 BB (AA, AB, BA, BB). Embryos were vitrified.
using High Security straws (Cryo-Bio-System) combined with DMSO-EG-S as cryoprotectants (Irvine Scientific Freeze Kit ©). The same kit was used for the warming process.

In case of fresh embryo transfer, patients began vaginal progesterone Progestan® (200 mg Bezins France, 1 capsule, 3 times a day) from the evening of the retrieval and oral estradiol Provames® (2 mg Merus Luxembourg, 2 tabs BID) starting on the day of embryo transfer. The single or double embryo transfer was performed at day 2 or 5, under transabdominal ultrasound guidance using a soft catheter.

In the case of a frozen embryo transfer, patients were seen approximately one month later. They received oral estradiol Provames® provenance (2 mg, 1 tab BID from day 1 to 4, then 1 tab in the morning and 2 in the evening from day 5 to 9 then 2 tabs BID) thereafter.

Endometrial thickness was monitored on transvaginal ultrasound and serum progesterone was measured to rule out premature ovulation before initiation of progesterone treatment. Endometrial thickness had to be >7mm, and progesterone less than 1.5 ng/ml. Progesterone administration consisted of a combination of subcutaneous injections of progesterone (Progiron® Genevrier France) 25 mg once daily and 2 vaginal progesterone capsules BID (Progestan®) (200 mg) starting 5 days before the transfer. On the sixth day of progesterone administration, one or two warmed blastocysts were transferred. When more than one embryo was available, the choice was made based on morphological grading. The frozen embryo transfer was performed under transabdominal ultrasound guidance using a soft catheter. Daily estrogen and progesterone administration were continued until the pregnancy test. Hormone administration was continued until the expected lutheo-placental shift, at 9 weeks of gestation.

STATISTICAL ANALYSIS

All continuous data were described with mean ± standard deviation and compared with Student test if the distribution was Gaussian and with the Mann-Whitney test if was not. P value <0.05 was considered as significant. All analyses were performed using SAS software (version 9.4; SAS Institute, Carry, NC). We categorized paternal age into 2 groups: <45 years and ≥45 years. To evaluate effect modification by maternal age, we stratified by maternal age <35 years, 35 to 38 years, and >38 years at cycle start.

Results

We report 2,358 couples who met the inclusion criteria. The average male age was 38.14 years, and the average female age was 35.09 years. The vast majority (86.6%) of reported cycles occurred with men aged <45 years, with only 13.4% of cycles involving men aged ≥45 years (table 1). Sperm parameters were comparable between the two groups, even if abnormal semen parameters were more prevalent in the group ≥45 years, the difference was not statistically significant. Tobacco consumption at the time of the stimulation was more common in the group <45 years, and men in the group ≥45 years were more likely to be non-smokers or former smokers. (Table 2)
Older paternal age was associated with older maternal age and therefore lower AMH and the use of higher doses of gonadotrophin. (Table 2)

Table 3 shows the results of the analysis for the primary outcome according to paternal age. The cLBR for male \(\geq 45\) (0.2857 ± 0.4525) was lower than in the group <45 (0.4714 ±0.4993), p<0.001 and also the results of the analysis for the secondary outcome cPR. The cPR for male \(\geq 45\) (0.311 ± 0.4637) was lower than in the group <45 (0.5301 ± 0.4992), p<0.001.

After stratification on maternal age, presented on table 4, cLBR was lower in the group \(\geq 45\) (0.26 ± 0.44), p = 0.061 for female > 38 and for female between 35-38 years (0.3 ± 0.46 vs 0.44 ± 0.5), p = 0.031. cPR was also lower in the group \(\geq 45\) (0.21 ± 0.41) than in the group <45 (0.34 ± 0.47), p < 0.001 for female > 38 and for female between 35-38 years (0.34 ± 0.48 vs 0.49 ± 0.5), p =0.036. When the analysis was restricted to cycles with maternal age <35 years the result was not statistically significant, cLBR was 0.59 ± 0.49 in the group \(\geq 45\), and 0.58 ± 0.49 in the group <45, p = 0.948; and cPR was 0.62 ± 0.49 in the group \(\geq 45\) and 0.64 ± 0.48 in the group <45, p = 0.785.

Regarding the secondary outcome: miscarriage rate, we found lower rate in the group \(\geq 45\) (0.041 ± 0.199) vs. in the group <45 (0.0788 ± 0.269) p = 0.02. (Table 3).

Same statement for female >38, miscarriage rate was 0.0153 ± 0.1231 in the group \(\geq 45\), and 0.0883 ± 0.284 in the group <45, p<0.001. When the analysis was restricted to cycles 35-38, miscarriage rate was higher in the group \(\geq 45\) (0.0656 ± 0.2496) vs. in the group <45 (0.0567 ± 0.2315), p = 0.779; and same statement for female < 35 (0.1034 ± 0.3072 in the group \(\geq 45\) vs 0.0847± 0.2786 in the group <45, p = 0.621). (Table 4)

Discussion

Our result indicates that in fresh or frozen IVF or ICSI cycles performed at Foch hospital between 2016 and 2020, advanced paternal age (\(\geq 45\) years old) was associated with lower cPR and cLBR. When the analysis was limited to female <35 years old, results were not significantly influenced by paternal age. These findings suggest that oocytes from female <35 years of age could correct sperm anomalies impacting fertility in case of advanced paternal age. Miscarriage rates were lower with advanced paternal age. When the analysis was restricted to female £38 a trend towards a reduction in the number of miscarriages appeared in the group <45 but not in a statically significant way.

Our findings are consistent with the results of several studies. In a retrospective cohort study, among 77,209 fresh IVF cycles, compared with paternal age <45 years, paternal age \(\geq 46\) years was associated with a lower likelihood of pregnancy per ART cycle (adjusted risk ratio [aRR] 0.81; 95% confidence interval [CI] 0.76–0.87) and per transfer (aRR 0.85; 95% CI 0.81–0.90), as well as a lower likelihood of live birth per cycle (aRR 0.76; 95% CI 0.72–0.84) and per embryo transfer (aRR 0.82; 95% CI 0.77–0.88) after controlling for maternal age and other potential confounders. When restricted to women aged <35 years,
no significant differences in the rates of live birth or miscarriage among couples in which the men were aged ≥45 years emerged compared with those aged ≥46 years (6).

In the retrospective cohort study published in 2019 and conducted which analyzed 2,425 cycles of couples, there was a gradual negative effect of male age and female age on live birth as odds ratios (OR) with 95% CI for each additional year of age (OR-male age: 0.96 [0.94–0.98]; OR-female age: 0.90 [0.88–0.93] \( p < 0.001 \)). Secondary outcomes showed a significant reduction in the odds of clinical pregnancy (OR-male age: 0.97 [0.96–0.99]; OR-female age: 0.92 [0.89–0.94] \( P < 0.001 \)) and an increase in the odds of miscarriage with greater age: male age (OR: 1.05 [1.01–1.08]; \( P = 0.002 \)); female age (OR: 1.11 [1.05–1.18]; \( P < 0.001 \)) (7).

More recently, several reports have investigated the parental origins of chromosomal imbalances. Bonus et al. evaluate the relationship between paternal factors and embryonic aneuploidy of paternal origins, specifically paternal age. There was no statistically significant correlation between paternal age and incidence of aneuploidy of paternal origins. However, it is interesting to see a trend in the association of aneuploidy of paternal origin, with increasing paternal age. Particularly in the case of age, the \( P \) value closely approached significance (18).

Several confounding factors must be taken into account when evaluating the influence of paternal age on ART results beyond the fact that this is a study using genetically unscreened embryos. First, male infertility is an element to consider, independently of male age, as it has been shown that the severity of male factor influences ART outcomes (19). Second, environmental considerations must be considered, such as the use of alcohol, smoking, medications with a gonadotoxic effect, obesity, and other comorbidities that may impact ART outcomes (20). Third, maternal age as confounding factor should be considered, as the age of female has a prominent role on ART outcomes. The perfect model to independently assess paternal age impact would be to use oocytes from oocyte donors, in order to avoid a bias related to oocyte quality. Indeed, the oocyte donor population are young women without fertility problems. Unfortunately, few studies evaluated the impact of paternal age in the oocyte donor population.

Begueria et al. in an egg donation model with ICSI as fertilization method, found that male age was not associated with any pregnancy outcome: biochemical pregnancy rate (RR: 1.0; 95% ci: 0.96-1.05), miscarriage rate (RR: 1.06; 95% ci: 0.94-1.03), ongoing pregnancy rate (RR: 0.98; 95% ci: 0.94-1.033), and LBr (RR: 0.98; 95% ci: 0.94-1.03) (9).

In their Study Dviri et al. (20) evaluated over 3,000 embryos derived from cycles using oocytes donor from women aged <33 years, and stratified by paternal (<39, 40-49, >50). No association was found between paternal age and aneuploidy rates. Advanced paternal age >50 compared with younger paternal age was associated with a lower fertilization rate and an increased rate of segmental aberration (21).

The clinical relevance of increased segmental aneuploidy in older males has yet to be explored. Sperm DNA fragmentation is more common in older men (22), and it could potentially be an explanation for why
segmental changes affect the paternal chromosomes at older ages. Further studies evaluating DNA fragmentation and paternal segmental aneuploidy would be worthwhile (23).

Our study also holds a result that we cannot readily interpret. Miscarriage rates were lower with advanced paternal age. When the analysis was restricted to female <38 a trend towards a reduction in the number of miscarriages appeared in the group <45 but not in a statically significant way. These findings seamlessly unexcepted may only represent a statistical fluke, but for sake of thoroughness they are reported here.

This study bears limitations: the miscarriage rate found in the group of male <45 years is higher than in the group of males over 45 years of age. By looking at the stratified study on female’s age, we can notice that this effect is only present on female >38 years. This difference, while counter-intuitive, could be explained through the repartition of ages within each category. 487 females over 38 were associated with young males (23.8%), and 196 with older males (62.3%). Also, by looking at the standard deviation we notice a higher difference between the two groups of males (³45 years and <45 years) in the category of female >38 years than in the other group of females. Data have been continuously verified in the male population, meaning without any split between the two groups and with a cut-off at 45 years of age, and this difference is not highlighted in the miscarriage rate observed. Furthermore, another data-check has been performed using a different cut-off at 40 years instead of 45 years, and once again the difference in the miscarriage rate has not been highlighted.

**Conclusion**

In couples undergoing ART procedures for infertility, advanced paternal age is associated with a lower cPR and cLBR in ART. We believe that our data add relevant information for understanding certain ART failures, emphasizing the role of considering both female and male age when assessing ART outcome.

**Declarations**

**Funding statement:** no funding available for this project

**Disclosure Statement:** Authors have nothing to disclose

**Author Contributions:** Conceptualization: Farabet Clemence, Paul Pirtea, Dominique de Ziegler; Methodology: Farabet Clemence, Paul Pirtea, Jean Marc Ayoubi; Formal analysis and investigation: Farabet Clemence, Alexandre Vallee, Claire Marchiori, Achraf Benammar; Writing - original draft preparation: Clemence Farabet, Paul Pirtea, Dominique de Ziegler; Writing - review and editing: Paul Pirtea, Dominique de Ziegler, Achraf Benammar; Supervision: Jean Marc Ayoubi

**Funding statement:** no funding available for this project

**Disclosure Statement:** Authors have nothing to disclose
Attestation Statement: Data regarding any of the subjects in the study has not been previously published.

Data Sharing Statement: Data will be shared with other researchers if reasonable requirement for further analysis is made.

References


Tables

Table 1: Repartition of male and female patients by age group

<table>
<thead>
<tr>
<th></th>
<th>male</th>
<th>&lt;45</th>
<th>%</th>
<th>≥45</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>female</td>
<td>&lt;35</td>
<td>1062</td>
<td>51.9</td>
<td>58</td>
<td>18.4</td>
</tr>
<tr>
<td></td>
<td>35–38</td>
<td>494</td>
<td>24.3</td>
<td>61</td>
<td>19.3</td>
</tr>
<tr>
<td></td>
<td>&gt;38</td>
<td>487</td>
<td>23.8</td>
<td>196</td>
<td>62.3</td>
</tr>
</tbody>
</table>
Table 2: Selected variables parameters: tabaco consumption (yes or no or former smoker), sperm parameters (normal, moderate OAT, severe OAT, extremely severe OAT), female age, female AMH, gonadotrophin dose during the stimulation, in the two male groups <45 and ≥ 45 years of age.

<table>
<thead>
<tr>
<th>AGE male</th>
<th>&lt;45</th>
<th>≥45</th>
<th>P VALUE</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N</td>
<td>% or SD</td>
<td>N</td>
</tr>
<tr>
<td>TABAC MALE</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>NO</td>
<td>1161</td>
<td>61.27 %</td>
<td>189</td>
</tr>
<tr>
<td>yes</td>
<td>420</td>
<td>22.16 %</td>
<td>46</td>
</tr>
<tr>
<td>former smoker</td>
<td>314</td>
<td>16.57 %</td>
<td>55</td>
</tr>
<tr>
<td>SPERM PARAMETERS</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>NORMAL</td>
<td>1642</td>
<td>80.37 %</td>
<td>252</td>
</tr>
<tr>
<td>LIGHT OAT</td>
<td>169</td>
<td>8.27 %</td>
<td>22</td>
</tr>
<tr>
<td>SEVERE OAT</td>
<td>133</td>
<td>6.51 %</td>
<td>22</td>
</tr>
<tr>
<td>EXTREMELY SEVERE OAT</td>
<td>99</td>
<td>4.85 %</td>
<td>19</td>
</tr>
<tr>
<td>AGE female</td>
<td>34.6</td>
<td>4.305 sd</td>
<td>38.32</td>
</tr>
<tr>
<td>AGE male</td>
<td>36.41</td>
<td>4.467 sd</td>
<td>49.33</td>
</tr>
<tr>
<td>AMH</td>
<td>3.117</td>
<td>2.965 sd</td>
<td>2.513</td>
</tr>
<tr>
<td>GONADOTROPHIN DOSE</td>
<td>4268</td>
<td>1937 sd</td>
<td>4912</td>
</tr>
</tbody>
</table>

Table 3 Results (cLBR, cPR, Miscarriage rate) of the primary and secondary outcomes, also cLBR and cPR and miscarriage rate in the two male groups <45 and ≥ 45 years of age.

<table>
<thead>
<tr>
<th>MALE</th>
<th>&lt;45</th>
<th>≥45</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N = 2043</td>
<td>N = 315</td>
</tr>
<tr>
<td>Mean</td>
<td>Std Dev</td>
<td>Mean</td>
</tr>
<tr>
<td>cLBR</td>
<td>0.4714</td>
<td>0.4993</td>
</tr>
<tr>
<td>cPR</td>
<td>0.5301</td>
<td>0.4992</td>
</tr>
<tr>
<td>Miscarriage RATE</td>
<td>0.0788</td>
<td>0.269</td>
</tr>
</tbody>
</table>

Table 4 Results of stratified analysis: cLBR and cPR and miscarriage rate in the two male groups < 45 and ≥ 45 years of age, stratified by female’s age < 35, 35-38, > 38 years of age.
<table>
<thead>
<tr>
<th>AGE MALE</th>
<th>&lt; 45</th>
<th>≥ 45</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>cLBR</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;35</td>
<td>0.58 (0.49)</td>
<td>0.59(0.49)</td>
<td>0.948</td>
</tr>
<tr>
<td>35 – 38</td>
<td>0.44 (0.50)</td>
<td>0.30 (0.46)</td>
<td>0.031</td>
</tr>
<tr>
<td>&gt;38</td>
<td>0.26 (0.44)</td>
<td>0.19 (0.39)</td>
<td>0.061</td>
</tr>
<tr>
<td>cPR</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;35</td>
<td>0.64 (0.48)</td>
<td>0.62 (0.49)</td>
<td>0.785</td>
</tr>
<tr>
<td>35 – 38</td>
<td>0.49 (0.50)</td>
<td>0.34 (0.48)</td>
<td>0.036</td>
</tr>
<tr>
<td>&gt;38</td>
<td>0.34 (0.47)</td>
<td>0.21 (0.41)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>MISCARRIAGE RATE</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;35</td>
<td>0.0847 (0.2786)</td>
<td>0.1034 (0.3072)</td>
<td>0.621</td>
</tr>
<tr>
<td>35 – 38</td>
<td>0.0567 (0.2315)</td>
<td>0.0656 (0.2496)</td>
<td>0.779</td>
</tr>
<tr>
<td>&gt;38</td>
<td>0.0883 (0.284)</td>
<td>0.0153 (0.1231)</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

**Figures**

**Figure 1**

cLBR (calculated after all embryos were transferred or until the obtention of the first LB) in the two male groups <45 and ≥45 years of age, stratified by female's age <35, 35-38, >38 years of age.
Figure 2

cPR in the two male groups < 45 and ≥ 45 years of age, stratified by female’s age < 35, 35-38, >38 years of age. Pregnancy rate defined as the presence of cardiac activity at the time of the first ultrasound approximately 7-8 weeks after the embryo transfer. Calculated after all embryos were transferred or until the obtention of the first LB.