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Original article

Neither male age nor semen parameters influence clinical pregnancy or live birth outcomes from IVF

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ABSTRACT

Advanced age is an increasing trend for both males and females seeking in vitro fertilization (IVF). This retrospective cohort study investigated the outcomes of 1280 IVF-related treatment cycles, selecting the first treatment for couples utilizing autologous gametes and who underwent single fresh embryo transfer. Males aged 40–49 years had a 52% reduction in normal sperm motility, while it was markedly reduced by 79% at 50 years or older. However, neither semen parameters nor male age were predictive of clinical pregnancy or live birth chance. In a combination of age groups, cases with Younger Females had the greatest chance of successful outcomes and this was independent of having a younger or older male partner. Specifically, Young Female-Young Male combinations (≤ 35 years) were the most likely to succeed in achieving a clinical pregnancy or live birth (OR 2.84, $p < 0.0005$ and 3.34, $p < 0.0005$, respectively), while the Young Female-Old Male group (≤ 35 and > 35 years, respectively) had a similar increased chance (OR 2.07, $p < 0.0005$ and 2.78, $p < 0.0005$, respectively). This trend strengthened as the Female age cut-off was increased to 38 years and the Male age cut-off increased to 40 or 42 years. Consistently, the groups comprising a Young Female with either a Young Male or Old Male outperformed the groups with an Old Female. Our finding confirms reduced fecundity with advancing female age as the most important parameter. The outcomes were not significantly influenced by semen parameters or male age with respect to the likelihood of clinical pregnancy or live birth.

1. Introduction

Along with female age, the age of males is also increasing among couples undertaking assisted reproductive techniques (ART) [1]. This could be associated with increased life expectancy, delayed parenthood and various socio-economic circumstances. The effect of maternal age on reproductive outcome has been well established, however the effect of male aging on ART outcomes remains largely understudied [2].

Analysis of semen quality is frequently used as a measure of male fertility. While there are reports of a decline in sperm parameters with increasing age [2,3], the effect of this in ART is reported from only a few studies. An early report showed that increasing male age was associated with decreased ejaculate volume, increased abnormal sperm morphology and reduced motility [4]. Subsequently, several retrospective studies revealed that lower semen volume, lower progressive motility and lower percentage of normal morphology were present in older men [5,6]. This was also echoed by another large prospective study [7].

It has been found that male aging may compromise spermatogenesis [8], leading to sperm damage through excessive production of reactive oxygen species [9,10]. It was also demonstrated that DNA fragmentation was increased in men over 45 years old, and almost double compared to younger men under 30 years old [11]. Other studies refute those findings, and detected no significant difference in the motility, morphology and DNA fragmentation profile with increasing male age [12].

Sperm DNA integrity is paramount for successful in vitro fertilization (IVF) and normal embryonic development. Increased male age has been linked with changes in epigenetic factors, with alterations at the molecular level leading to negative effects on post fertilization development [13]. In terms of pregnancy and live birth rates, several studies have indicated an inverse relationship between increasing male age and

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outcomes in both IVF and GIFT cycles [14]. In a separate study, comparison of the IVF outcomes in two groups showed that the fertilization, cleavage, blastulation and clinical pregnancy rates were all lower in the advanced paternal age group [15]. In view of these negative effects, the American Society for Reproductive Medicine [16] and the British Andrology Society [17] recommended that semen donation should be restricted to men aged less than 40 years.

Interestingly, the additive effects of combined maternal and paternal age on pregnancy and live birth rates was recently investigated by one Australian facility [18]. They concluded that paternal age did not correlate significantly with clinical pregnancies or viable pregnancy. However, there was a 10% decrease in pregnancy and live birth rates in women aged 35 years when their male partner was aged above 40 years, implying an interactive effect.

As the number of studies on paternal age is limited and the results discrepant, there seems to be no clear consensus regarding the independent effect of male age on reproductive outcomes. As more couples of advanced reproductive age seek fertility treatment, it is vital to explore and understand the effects of paternal age on pregnancy and livebirth outcomes, as well as examining the relationship with underlying semen parameters.

2. Methodology

2.1. Study cohort

This study is a retrospective cohort study of all new IVF treatment cycles from 1st April 2008 to 30th November 2017 conducted at one facility and registered at ACTRN12618001820291. The specified cut-off date enabled all resulting pregnancies to be tracked through to delivered outcomes. We included only the first IVF cycles among new heterosexual couples, that utilized autologous gametes (oocytes and spermatozoa) and who underwent single embryo transfer (SET). We excluded all frozen embryo transfer cycles as well as other cycles such as natural cycles. Donor cycles, utilizing donor sperm, oocytes or embryos were excluded to reduce the bias from multiple confounders. Cycles that underwent embryo biopsy with preimplantation genetic screening were also excluded. The study cohort comprised of couples referred to fertility specialists due to issues with conceiving naturally, and were therefore considered sub-fertile. With investigation, the vast majority of these couples had unexplained infertility (61.8%), while male factor cases excluding azoospermia, constituted 22.4% of cases analysed (Supplement Table 1).

2.2. Clinical protocols for IVF

The IVF protocol types (flare, antagonist, long down regulation, AACEP) were strictly conducted according to the published PIVET rFSH dosage algorithms [19], which is based on female age, body mass index (BMI), antral follicle count (AFC) and anti-Mullerian hormone (AMH) level. Oocyte maturation trigger (either human chorionic gonadotrophin or GnRH agonist) and luteal phase support was also based on the algorithm according to the number of developing follicles and retrieved oocyte number. Oocyte recovery was performed 36–37 h post trigger injection via transvaginal oocyte aspiration (TVOA) using either a single lumen 17 gauge needle (for ≥ 5 follicles) or double lumen 16 gauge needle (for < 5 follicles). The recovered oocytes were fertilized and cultured until Day 3 or extended to Day 5 blastocyst stage, if there were at least 3 good-quality embryos on Day 3. The patients then had SET either with cleavage or blastocyst stage embryos, depending on the outcome of embryo culture.

2.3. Laboratory protocols for IVF

All oocytes were graded at collection and allocated to designated insemination method (i.e. IVF Only, ICSI Only or IVF-ICSI Split) according to previously reported criteria [20]. The oocytes then had fertilization checks for pronuclei 16–18 h post overnight incubation. Oocytes at germinal vesicle stage or M1 stage were discarded. Degenerated oocytes or those with fractured zona were also eliminated. Day-3 embryos were graded using a four-point system, with half point increments as previously published [21]. Day-5 embryos were graded using the Gardner scoring system for blastocysts [22]. The best quality embryo was then transferred as per protocol, the remainder committed to cryopreservation by vitrification.

2.4. Statistical aspects

The data including demographics, sperm parameters and pregnancy outcomes were analyzed using ANOVA, Chi-square test and within both univariate and multiple logistic regression models applying SPSS v25. The semen/sperm parameters were categorized according to the WHO criteria into two groups for statistical analysis. The normal parameters were defined as sperm concentration ≥ 15 million/ml, sperm motility $\geq 32\%$ for grade A and B, sperm morphology $\geq 4\%$ and DNA fragmentation index $\leq 15\%$. High grade embryos included high quality Day 3 cleavage stage and high quality blastocyst stage embryos.

2.5. Ethical considerations

This is a retrospective study of routine clinical practice conducted under license from the Reproductive Technology Council (RTC) of Western Australia and the Reproductive Technology Accreditation Committee under the auspices of the Fertility Society of Australia. Therefore, specific ethics approval was not required. However, analysis and reporting of the data was granted by Curtin University Human Research Ethics Committee approval RD-25-10.

3. Results

The data analysis of the final cohort was applied to 1280 cases inseminated by IVF Only (N = 115), ICSI Only (N = 1063) and those cases having an IVF-ICSI split insemination (N = 102) (Fig. 1). The clinical pregnancy rate per embryo transfer (ET) for each insemination group was 40.9, 33.4 and 45.1%, respectively, while the live birth rate per ET was 33.9, 25.8 and 35.3%. The clinical pregnancy and live birth rate according to method of insemination of the transferred embryo was 43.3% and 33.8% (i.e. IVF versus ICSI) and 35.7% and 26.1%, respectively, and the insemination method did not significantly influence outcomes (data not shown). In order to demonstrate the overall relationship between age (both male and female) and live birth outcome, the age of each parent was independently plotted against live birth rate (Fig. 2). The data revealed that live birth rates were highest for females up to age group 31–32 years (36%), decreasing to 30% and 26% for those aged 33–34 years and 35–36 years, respectively, and thereafter declining further in a stepwise fashion (Fig. 2). For males, the trend according to age was slightly different, staying relatively stable at approximately 35% as far as 33–34 years, the, dropping slightly to 30% and 20% for those aged 35–36 years and 37–38 years respectively (Fig. 2). However, after 38 years the live birth rate appeared to plateau at around 25%, with a further decrease to 18% when aged 43 years and above, by which stage live births for females were very low at 3%.

The relationship between male age and semen parameters was investigated using logistic regression analysis (Table 1). There was no significant association between male age groups and sperm concentration, morphology, DNA fragmentation index (DFI) and the likelihood of generating high quality embryos. However, there was a significant decrease in sperm motility with advancing male age. Specifically, males between 40–49 years had a 52% reduced chance to have normal sperm motility ($\geq 32\%$ progressively motile sperm), while males 50 years or older had a 79% reduced chance for normal motility.

In a binary logistic regression model, semen parameters did not

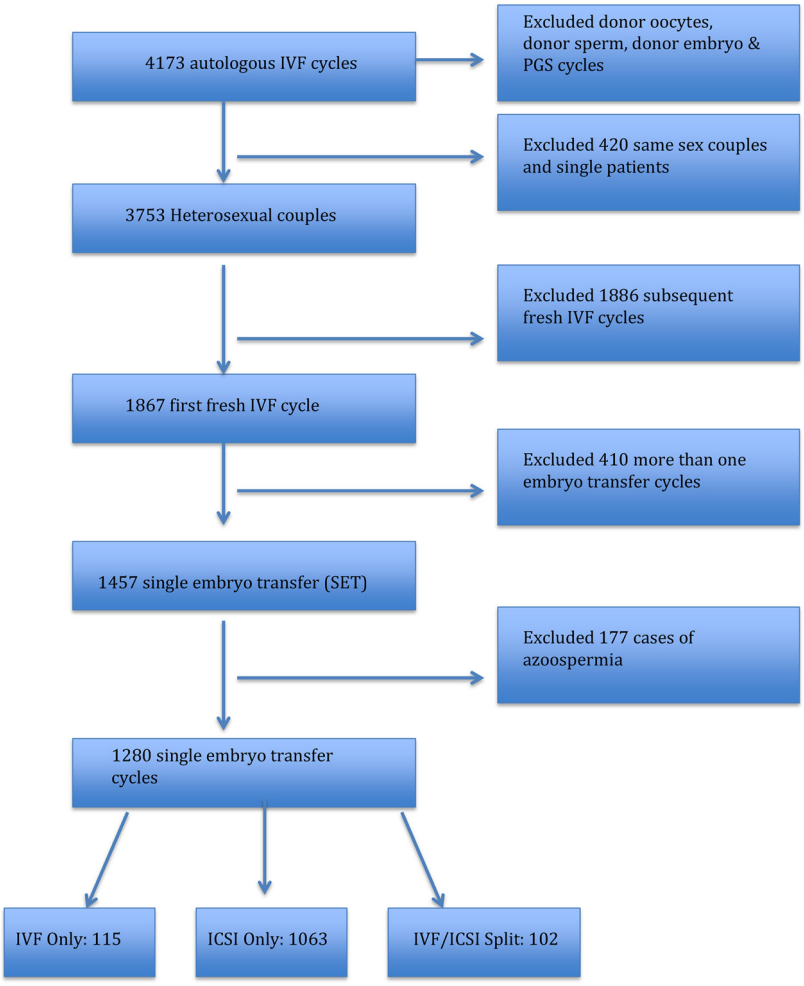

Fig. 1. Flow diagram of patient data extraction and analysis.

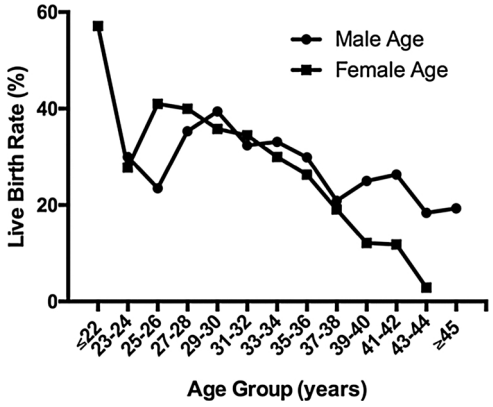

Fig. 2. Live birth rates plotted according to male or female parent age.

independently predict clinical pregnancy or live birth chance (Table 2). No significant relationship was observed between clinical pregnancy or live birth chance and sperm concentration, motility, morphology or DFI (Table 2). Male age as a continuous independent variable was also not associated with prediction of outcomes. However, female age was independently predictive of clinical pregnancy and live birth chance. In multiple logistic regression models for clinical pregnancy and live birth chance, again female age was the only significant independent variable (Table 2). Of note, in the multiple regression model, there was a trend towards sperm motility impacting on a lower chance of live birth, although this was not significant (OR 0.58, 0.33–1.02, $p = 0.060$).

An extended analysis of male age as a categorical variable showed that males aged 40–44 years had a 48% and 51% reduction in the chance of achieving a clinical pregnancy and live birth respectively, compared to those < 30 years (Table 3). This chance was reduced further at the age of 50 years or greater when likelihood of successful clinical pregnancy and live birth decreased by 55% and 64% respectively. However, following adjustment for female age in a multiple logistic regression analysis, male age as a categorical variable became insignificant (Table 3).

Finally, the study next focused on whether combinations of female and male age groups using specified age cut-offs, led to a significantly different likelihood of clinical pregnancy or live birth success. In all cases with a Younger Female, the chance of successful clinical pregnancy and live birth was significantly greater in comparison to all combination groups with an Older Female, either with a Young or Old Male partner (Table 4). The OR for the Younger Female combinations ranged from 2.07 to 4.31 for clinical pregnancy and live birth chance, and all were statistically significant (Table 4). This was observed across all age group cut-offs. Specifically, using ≤35 and > 35 years for both the male and female as “Young” and “Old” criteria, and using the Old Female-Old Male group as the reference category, the Young Female-Young Male combination were the most likely to succeed in achieving a clinical pregnancy or live birth (OR 2.84, $p < 0.0005$ and 3.34, $p < 0.0005$, respectively), while the Young Female-Old Male group had a similar increased chance (OR 2.07, $p < 0.0005$ and 2.78, $p < 0.0005$, respectively). This trend strengthened as the Female age cut-off was increased to 38 years and the Male age cut-off increased to

Table 1
Logistic regression analysis of the relationship between male age and semen parameters. The reference group was normal parameters which were defined as sperm concentration ≥15 million/ml, sperm motility ≥32% for grade A and B, sperm morphology ≥4% and DNA fragmentation index ≤15%. High grade embryos included high quality Day 3 cleavage stage and high quality blastocyst stage embryos as the reference category.

Male age (years)		Sperm Concentration		Sperm Motility		Sperm Morphology		DNA Fragmentation		High Grade Embryos	
	n	Univariate OR (95% CI)	*p-value*	Univariate OR (95% CI)	*p-value*	Univariate OR (95% CI)	*p-value*	Univariate OR (95% CI)	*p-value*	Univariate OR (95% CI)	*p-value*
< 30	118	1.00	–	1.00	–	1.00	–	1.00	–	1.00	–
30–39	740	0.91 (0.55–1.49)	0.707	0.60 (0.35–1.03)	0.062	0.87 (0.57–1.32)	0.507	0.78 (0.48–1.28)	0.331	1.12 (0.73–1.71)	0.614
40–49	349	1.06 (0.62–1.82)	0.830	0.48 (0.26–0.88)	0.017	0.76 (0.48–1.20)	0.241	0.91 (0.54–1.54)	0.719	0.80 (0.50–1.27)	0.337
≥50	73	1.17 (0.54–2.52)	0.699	0.21 (0.06–0.73)	0.015	0.57 (0.28–1.23)	0.105	0.69 (0.32–1.47)	0.336	0.54 (0.27–1.12)	0.098
Total	1280										

Table 2
Univariate and multiple logistic regression analysis of the impact of semen parameters and both male and female age (continuous variable) on clinical pregnancy and live birth chance.

Variable		Clinical Pregnancy Chance				Live Birth Chance			
		Univariate OR (95% CI)	*p-value*	Multiple Regression OR (95% CI)	*p-value*	Univariate OR (95% CI)	*p-value*	Multiple Regression OR (95% CI)	*p-value*
Sperm Concentration		0.99 (0.77–1.29)	0.935	1.20 (0.79–1.83)	0.387	0.85 (0.64–1.13)	0.254	0.99 (0.62–1.59)	0.958
Sperm Motility		0.97 (0.75–1.27)	0.847	0.61 (0.36–1.02)	0.058	0.89 (0.67–1.19)	0.427	0.58 (0.33–1.02)	0.060
Sperm Morphology		1.10 (0.88–1.38)	0.395	0.84 (0.60–1.19)	0.328	0.93 (0.73–1.18)	0.559	0.92 (0.65–1.32)	0.660
DNA Fragmentation Index (%)	*≥30.0*	1.00	–	1.00	–	1.00	–	1.00	–
	5.0–14.9	0.86 (0.65–1.15)	0.316	0.84 (0.61–1.17)	0.307	0.84 (0.62–1.14)	0.269	0.81 (0.57–1.16)	0.248
	15.0–29.9	1.15 (0.79–1.68)	0.456	1.22 (0.80–1.84)	0.356	1.08 (0.72–1.60)	0.721	1.13 (0.72–1.75)	0.597
Female age		0.90 (0.88–0.93)	0.000	0.91 (0.89–0.94)	0.000	0.90 (0.87–0.93)	0.000	0.91 (0.88–0.94)	0.000
Male age		1.00 (0.98–1.02)	0.991	1.00 (0.97–1.02)	0.657	1.00 (0.98–1.02)	0.762	0.99 (0.97–1.02)	0.419

40 or 42 years (Table 4). Importantly, the inclusion of a Young Male with an Older Female combination did not increase the chance of a successful clinical pregnancy or live birth when compared to the corresponding Old Female-Old Male reference group, which indicated no beneficial or additive effect from a Younger male (Table 4). This was again observed across all age groups and cut-offs.

Additional supplementary logistic regression analysis showed that AFC and embryo quality were positively correlated with clinical pregnancy & live birth chance (Supplement Table 2). Higher AFC and better quality embryos were associated with better clinical pregnancy & live birth chance. However, in the multiple logistic regression model, only female age and embryo quality predicted clinical pregnancy and live birth chance (Supplement Table 2). The cause of sub-fertility was also not associated with significant changes in the chance for successful clinical pregnancy or live birth (Supplement Table 2). Male age was again shown not to be statistically significant. Finally, male and female BMI were also not significantly associated with the likelihood of clinical pregnancy or live birth success (Supplement Table 3).

4. Discussion

The decline in pregnancy and live birth rates has been well established with advancing female age [23], which is attributed to poorer oocyte quality [24,25] and increased chromosomal abnormalities [26] and conditions that may impair fertility including tubal disease, leiomyomas, and endometriosis with aging [27]. However, the male contribution is largely understudied with conflicting reports [28,29]. The literature has suggested that older men have reduced sperm quality, in terms of parameters such as concentration, motility, morphology and DNA fragmentation, and could possibly translate into poorer clinical pregnancy and live birth outcomes in IVF couples [28]. Our data revealed that older men have reduced sperm motility especially noted for men ≥ 50 years old and this was the only semen parameter associated with male age in our cohort. Surprisingly, these male sperm parameters did not affect clinical pregnancy rate and the live birth rates independently or in multiple regression models. Importantly, male age also did not play a role in determining production of high quality embryos, successful clinical pregnancy or live birth rates following adjustment for various confounders including female age and ovarian reserve.

In examining the question of an additive effect of different combinations of male and female age cut-offs, it was found that the Old Female-Young Male combination as well as the Old Female-Old Male combination had significantly lower clinical pregnancy and live birth

Table 3
Univariate and multiple logistic regression analysis of the impact of male and female age on clinical pregnancy and live birth chance.

Variable		Clinical Pregnancy Chance				Live Birth Chance			
		Univariate OR (95% CI)	*p-value*	Multiple Regression OR (95% CI)	*p-value*	Univariate OR (95% CI)	*p-value*	Multiple Regression OR (95% CI)	*p-value*
Male age (years)	*< 30*	1.00	–	1.00	–	1.00	–	1.00	–
	30–39	0.75 (0.51–1.11)	0.152	1.21 (0.79–1.85)	0.371	0.77 (0.51–1.16)	0.211	1.26 (0.81–1.95)	0.31
	40–49	0.52 (0.34–0.81)	0.003	1.32 (0.79–2.18)	0.289	0.49 (0.31–0.77)	0.002	1.24 (0.72–2.11)	0.441
	≥50	0.45 (0.24–0.84)	0.013	1.01 (0.51–2.02)	0.972	0.36 (0.17–0.74)	0.005	0.80 (0.37–1.73)	0.571
Female age		–	–	0.90 (0.88–0.93)	0.000	–	–	0.90 (0.87–0.93)	0.000

Table 4
Univariate and multiple logistic regression analysis of the impact of male and female age group combinations on clinical pregnancy and live birth chance.

Variable		Clinical Pregnancy Chance		Live Birth Chance	
		Univariate OR (95% CI)	*p-value*	Univariate OR (95% CI)	*p-value*
Female: ≤35 & > 35 years: Male: ≤35 & > 35 years	*Old Female Old Male*	1.00	–	1.00	–
	Old Female Young Male	1.13 (0.63–2.02)	0.683	1.41 (0.74–2.69)	0.296
	Young Female Old Male	2.07 (1.50–2.87)	0.000	2.78 (1.93–3.99)	0.000
	Young Female Young Male	2.84 (2.11–3.83)	0.000	3.34 (2.39–4.68)	0.000
Female: ≤38 & > 38 years: Male: ≤40 & > 40 years	*Old Female Old Male*	1.00	–	1.00	–
	Old Female Young Male	0.77 (0.36–1.65)	0.495	0.65 (0.25–1.74)	0.396
	Young Female Old Male	2.93 (1.76–4.90)	0.000	3.13 (1.72–5.70)	0.000
	Young Female Young Male	3.11 (1.98–4.89)	0.000	3.75 (2.19–6.43)	0.000
Female: ≤38 & > 38 years: Male: ≤42 & > 42 years	*Old Female Old Male*	1.00	–	1.00	–
	Old Female Young Male	1.32 (0.64–2.70)	0.450	1.01 (0.42–2.43)	0.982
	Young Female Old Male	3.75 (2.00–7.01)	0.000	3.32 (1.61–6.86)	0.001
	Young Female Young Male	3.91 (2.27–6.74)	0.000	4.31 (2.28–8.15)	0.000

rates than the Young Female-Young Male population. However, for women > 35 years, the inclusion of a younger male (≤35 years) did not significantly improve the likelihood of clinical pregnancy or live birth success, even though the OR increased very slightly. This was evident across all age cut-offs, which indicated that the influence of paternal age was negligible. The data suggested that female age was the single most dominant factor to predict the embryo quality as well as clinical pregnancy and live birth rates. Nonetheless, advancing male age affected sperm motility, but this was not important enough to alter the embryo quality nor either clinical pregnancy or live birth rates.

The additive effect of a 'Young' or 'Old' male and female has only recently started to be investigated [18]. In this recent study, there was an additive negative effect on pregnancy and live birth rates when both partners were of advanced age [18]. The authors reported a 10% decrease in pregnancy and live birth rates in women aged 35 years when the male partner was above 40 years, compared with a partner who was less than 30 years old. However, male age did not worsen the prognosis for the younger woman in the current study and a young male did not provide a beneficial or 'protective' effect on the chances of success in the older women. This needs to be considered in the light of our clinical policy where the vast majority of cases (83%) at our facility are undertaken with ICSI [20], and all new cases are directed towards an IVF-ICSI Split model. Like the recent study [18], we investigated the influence of insemination method on outcomes, and also found it did not significantly alter clinical pregnancy or live birth chance independently. IVF fertilization was used in approximately 9% of transfers in the current cohort and consequently our sample size was severely unbalanced to accurately answer this question. Nonetheless, it may be the case that this clinical approach of high ICSI insemination may reduce the impact of older paternal age on clinical outcomes, and possibly raises the question whether advanced male age should be considered as an additional factor for ICSI insemination. Data in most studies on clinical reproductive outcome of older sub-fertile men are difficult to interpret because of the lack of adjustment for female age.

Autologous IVF in women aged 45 with acceptable ovarian reserve carries very low prognosis. Female patients aged 46 and older should be counseled appropriately such that a live birth is highly unlikely being < 1% per initiated cycle [30,31]. This group of patients would improve their chances of live births greatly by receiving donor oocytes from a younger woman, or even having their own embryos transferred when generated at a younger age [31]. Current literature has shown that older women with younger donor oocytes have higher clinical pregnancy and live birth rates commensurate with the age of the donor [32]. This has implications for the quality of embryos transferred.

Our analysis showed that the high and medium quality blastocysts, early blastocysts and high quality Day 3 cleavage-stage embryos were all significantly associated with improved clinical pregnancy rate and live birth rates. This remained significant after controlling for male age. This may suggest that the female component of the embryo, which is the oocyte, may be the predominant factor in determining the final quality of the embryo, and thus optimum clinical pregnancy and live birth rates thereafter. The reduced quality of oocytes associated with female age has been well-established, and the current study echoes these findings.

However, it appears that the male counterpart has a lesser role to play in embryo quality and overall outcomes. Our results concur with other studies that show no correlation between male age and clinical pregnancy and live birth rates [33,34]. It was shown that advanced male age slightly impairs semen quality, but this effect does not lead to a poorer outcome in assisted conception when the female partner is not of advanced age [35]. Therefore, male age as a prognostic factor in assisted reproduction may not be a relevant variable.

While very few studies have investigated the combined impact of male and female age on IVF outcomes, and the current study offers evidence to indicate that female age is the more important player, there are some limitations associated with this analysis. The study has been retrospectively derived from a large database, and as such is exposed to the various biases associated with retrospective analysis. The authors have endeavoured to offset any perceived case-selection bias by analyzing only the first IVF cycle for each couple during the study period and included a variety of potential confounding parameters analysed in order to be as comprehensive as possible, in determining the independent effect of male age and semen parameters on IVF outcomes. In addition, this analysis has been conducted in a sub-fertile cohort and may have limited extrapolation to general populations.

The major findings from this study will further strengthen the evidence that delaying childbearing in women has more serious implications than males delaying. Assisted reproductive technology should not be seen as the answer to fertility problems in women of advanced age as the results for both clinical pregnancy as well as live birth rates reduce significantly even in the advent of improved technology in human reproduction; with an absolute cut-off for autologous treatments at age 45 years [31].

Author contributions

UM, KNK, and PMH extracted the data which was analysed by UM, KNK and SSD. UM wrote the first draft of the manuscript which was revised by KNK, PMH, SSD and JLY. The study was supervised by JLY.

Conflicts of interest

All authors declare there are no conflict of interests.

Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at doi:https://doi.org/10.1016/j.repbio.2018.11.003.

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