Having a baby in your 40s with ART: the reproductive dilemma of autologous versus donor oocytes.

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ABSTRACT

Background: Increasing numbers of women ≥40 years are accessing assisted reproductive technology (ART) due to age-related infertility. There is limited population-based evidence about the impact on the cumulative live birth rate (CLBR) of women aged ≥40 years using their own oocytes, compared to women of a similar age, using donor oocytes.

Aims: Compare the CLBR for women ≥40 years undergoing ART using autologous oocytes and women of similar age using donor oocytes.

Materials and Methods: This population-based retrospective cohort study used data from all women aged ≥40 years undergoing ART with donated (n=987) or autologous oocytes (n=19 170) in Victoria, Australia between 2009 and 2016. A discrete-time survival model was used to evaluate the CLBR following ART with donor or autologous oocytes. The odds ratio, adjusted for woman's age; male age; parity; cause of infertility; and the associated 95% confidence intervals (CI), were calculated. The numbers needed-to-be-exposed (NNEs) were calculated from the adjusted odds ratio (AOR) and the CLBR in the autologous group.

Results: The CLBR ranged from 28.6% to 42.5% in the donor group and from 1.4% to 12.5% in the autologous group. The discrete-time survival analysis with 95% CI demonstrated significant AOR on CLBR across all ages (range AOR: 2.56, 95% CI: 1.62–4.01 to AOR: 15.40, 95% CI: 9.10–26.04).

Conclusions: Women aged ≥40 years, using donor oocytes had a significantly higher CLBR than women using autologous oocytes. The findings can be used when counselling women ≥40 years about their ART treatment options and to inform public policy.

Introduction

In recent years, there has been a shift towards later childbearing with the birth rates for women ≥40 years at 12.9 births per 1,000 women in 2017, compared to 4.4 births in 1980[1]. Reasons cited for this trend include improved access to reliable contraception, women's greater participation in education, developing a career, and the erroneous belief that ART can extend the reproductive lifespan[2-4]. The lack of a partner willing to commit to parenthood has also been cited as a reason for delayed childbearing[5]. Also, an increasing number of divorces and second marriages have contributed to more women in their forties desiring children[6]. Simultaneously, there has been an increase in the use of ART treatments by women ≥40 years. In Australia and New Zealand, almost a quarter (23.4%) of all ART treatment cycles in 2017 were undertaken by women aged ≥40 years compared to 16.1% in 2006[7].

Older women contemplating ART face the reproductive dilemma of choosing between using their own (autologous) or donor oocytes. Couples' motivations for using autologous oocytes include a strong desire to have a biologically related child[8]. However, in women ≥40 years, the risk of aneuploidy in oocytes may exceed 60%, thereby significantly contributing to low embryo implantation rates and low chances of a live birth[9]. To reduce the risk of aneuploidy and increase the likelihood of a live birth, women can use oocytes donated by a younger woman, ideally less than 35 years[10]. In Australia and New Zealand where commercial donation (donation with monetary compensation other than "out of pocket" expenses) is prohibited, there is a shortage of donor gametes and 36% of oocyte donors are ≥35 years[7]. Due to the shortage of women who are willing to donate oocytes to someone who is not known to them, using a family member or a friend as an oocyte donor may be the only alternative for some couples[11].

Whether using autologous or donor oocytes, the chance of having a baby is of fundamental interest to people who use ART. However, studies in the United Kingdom, United States and Australia show that the quality of information on ART clinic websites, about the chance of having a baby as a result of ART, is poor[12,13]. There are several different ways of presenting ART success rates with different authorities arguing for different approaches[14-16]. Malizia and colleagues contend that ART success rates presented as outcome per cycle or embryo transfer have limited value because they do not account for the additional chance offered by frozen embryo transfers resulting from a stimulated cycle[17]. The CLBR is advocated as a more useful way of presenting the chance of success for both patients and clinicians because it includes the added opportunity offered by frozen embryos and provides an overall estimate of the possibility of having a baby following one stimulated cycle[18].

The purpose of this population-based cohort study is to quantify the effect of using autologous or donated oocytes on the CLBR among women aged ≥40 years. The findings can be used when counselling women over 40 contemplating ART to help them and their partners make informed decisions about whether to use their own or donor oocytes.

Materials and Methods

Data

The data used in this study were collected from all ART providers in Victoria, Australia. The Victorian Assisted Reproductive Treatment Authority (VARTA) database includes information on the ART procedure (including the number of oocytes collected, donated and received; method of fertilisation; and whether fresh or thawed embryos were transferred), and the outcomes of ART procedures (including birth status, gestational age, birth weight and congenital anomalies). Data are collected annually from all ART clinics in Victoria.

This study used data from all women aged ≥40 years who had ART treatment between 1 July 2009 and 30 June 2016 of whom 987 had used donated oocytes, and 19,170 had used their own oocytes in 1,983 and 26,638 cycles respectively. Demographic characteristics, treatment types and outcomes were recorded for each completed cycle (fresh and associated thaw cycles) until a live birth was achieved or until 30th June 2016.

Study factors

The women's ages were calculated at the time of the first simulated cycle and categorised into eight groups: 40, 41, 42, 43, 44, 45, and ≥46 years. Male age was grouped as: <30, 30-34, 35-39, 40-44 and ≥45 years. Previous pregnancy of ≥20 weeks gestation was grouped as yes, no and not stated. Fertilisation procedure was either IVF or ICSI. Stage of embryo development was grouped into cleavage or blastocyst stage. The numbers of embryos transferred were grouped as one, two, three or more embryos.

Main outcome measure

The primary outcome was the cumulative live birth rate (CLBR), defined as at least one live birth per woman, following a stimulated cycle or oocyte donation and associated thaw cycles. A live birth was defined as a baby showing signs of life with gestational age ≥20 weeks or birthweight ≥400 grams. Multiple births were counted as one live birth. The observed CLBR was calculated over multiple transfers using the conservative assumption that women who did not return for treatment did not have a pregnancy resulting in a live birth.

Statistical analysis

Descriptive statistics were used for data on women's age, male partner age, history of previous pregnancy of ≥20 weeks gestation, fertilisation procedure, stage of embryo development and the number of embryos transferred. CLBR for each age group and cycle

numbers were calculated for both autologous and donor oocyte groups. A discrete-time survival model was used to evaluate the prognostic significance of ART treatment for the CLBR across age groups. The odds ratio, adjusted for the woman's age; male age; parity (nulliparous/parous); and cause of infertility (male only, female only, or unexplained); and its associated 95% CI were computed. Descriptive statistical analysis was performed using SPSS 25 (Armonk, NY, USA: IBM Corp.) and R version 3.4.1 was used for the discrete-time survival analysis. To facilitate clinical interpretation, results were also expressed as the number needed to be exposed (NNE), which has a similar definition to the popular summary statistic number needed to treat (NNT). In cohort studies, Bender & Blettner (2002) argue that the NNE is a preferable term when the considered agent is exposure rather than treatment[19]. In this study, the NNE is the average number of unexposed persons, i.e. women in the autologous oocyte group, needed to be exposed to donor oocytes, to observe one additional live birth[19]. The NNEs for all age groups were calculated from the adjusted odds ratios (AOR) and the CLBR for women in the autologous oocyte group, by means of the Bender & Blettner (2002) multiple logistic regression model[19].

Ethics

Ethics approval for this study was granted by the Human Research Ethics Committee of University of Technology Sydney, Australia (UTS HREC REF NO. ETH16-0800). Access to the VARTA data was granted by VARTA.

Results

Table I presents the characteristics of the study population. The majority of women in the autologous group were aged 40 – 44 years (93%) with very few (7%) women aged ≥45 years. In contrast, in the donor oocyte group, 62% of women were aged 40-44 years and 38% aged

≥45 years. The mean age of the oocyte donors was 33.7 years (range 21 to 45 years) with 49% aged 35 years and over. The rate of ICSI as the method of fertilisation was high in both groups (76% in autologous and 92.5% in the donor oocyte group).

<Insert Table I here>

Table II shows the number of embryos and the stage of the embryos at embryo transfer. The proportion of single and double blastocyst transfer was higher in the donor oocyte group than in the autologous group (49% versus 35% and 36% versus 24% respectively). Triple embryo transfer only occurred in the autologous group, with the majority of transfers at the cleavage stage (93%).

<Insert Table II here>

Table III displays the mean number of oocytes collected and the mean number of embryos suitable for transfer for freezing, per age group, in both the donor and autologous groups.

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Table IV displays the CLBR by age for the donor and autologous groups. In the donor group, the CLBR ranged from 28.6%(for women aged 40 years) to 42.5% (for women aged 44 years) and in the autologous group it ranged from 1.4% (for women aged 45 years) to 12.5% (for women aged 40 years). The discrete-time survival analysis with odds ratio (OR) and the associated 95% CI demonstrated that the donor oocyte group has a significantly higher CLBR than the autologous group across all ages. At ages 44, 45 and ≥46 women in the donor oocyte group were at least ten times more likely to have a live birth than women in the autologous group. Overall the likelihood of a live birth was five times greater in the donor oocyte group than the autologous group, or if expressed as an NNE result, on average six

women in the autologous oocyte group would need to receive donor oocytes to have one additional live birth.

<Insert Table IV here>

As shown in Table V, regardless of the recipient's age, women with donors aged ≥40 years had a significantly lower CLBR when compared to recipients with younger donors. The highest overall CLBR (42.5%) was seen in women with donors <35 years.

<Insert Table V here>

Over six transfers, the CLBR was consistently higher in the donor oocyte group than the autologous group. The increment in live births between cycle 2 and cycle 3 was 0.5% in the autologous and 3.3% in the donor oocyte group. The cycle specific and cumulative live birth rates (all ages) are presented in Table VI.

<Insert Table VI here>

Discussion

This population-based cohort study shows that most women in their forties who access ART use their own oocytes despite the minimal chance of having a baby as a result. Unsurprisingly, we found that, across all age groups, women using donor oocytes were five times more likely to have a live birth than women using autologous oocytes. We found however that recipients with donors aged 40 years or older had a significantly lower CLBR, regardless of the recipient's age. This confirms that the age of the oocytes is critical for the chance of success and lends support to the requirement for an upper age limit for oocyte donors[20]. In spite of the known low chance of success, the overwhelming majority of women used their own oocytes, likely reflecting people's preference for biologically related children, societal expectations of family

formation, the regulatory environment which only allows altruistic donation, a lack of donor oocytes, and funding arrangements for ART in Australia which do not impose age limits on women who wish to use their own oocytes.

The cost of ART has far-reaching implications on access and uptake of fertility treatment[21]. Australia is considered to have one of the most supportive funding arrangements for ART globally. Medicare, the Australian Government's universal health insurance scheme reimburses up to the 80% of costs incurred for ART, once a certain threshold has been reached, irrespective of the woman's age[21]. The few available studies on access to ART suggest that affordability is a powerful determinant of whether couples pursue treatment[21,22].

In Australia, the demand for donated oocytes exceeds supply[23], which may partly explain the high proportion of women in this study using their own oocytes in ART. Australian regulation only permits altruistic gamete and embryo donation[24,25]. Typically in Australia, women who need donor oocytes have to join long waiting lists due to a scarcity of donors, or access donated oocytes from clinics abroad such as The World Egg Bank which comply with Australian national regulation and state laws. However, most recipient couples rely on a friend or a relative to donate oocytes or find a donor through an online forum[11]. It has been suggested that oocyte donors should be compensated for the inconvenience and risk associated with donation, and this may increase the supply of donated oocytes in Australia. The Australian Human Ethics Committee, through public consultation, explored attitudes relating to compensation for egg donors during 2014 and 2015. A key question still under consideration is how much Australian oocyte donors should be compensated to make it worthwhile for them without being too high and potentially causing poor women to donate for financial reasons[24].

The desire to have a biologically related child may also be a reason why so many of the women in our study used their own oocytes. A number of studies show that both women and men over-estimate the ability of ART to compensate for any age-related fertility decline and believe that up until menopause, ART can assist most women to have a child using their own eggs[5,8,20,26]. The results of the current study highlight the need for fertility health promotion initiatives to improve awareness about the impact of age on fertility and the chance of spontaneous and ART conception. Hammarberg and colleagues argue that fertility health promotion in schools and primary care encounters can improve young people's understanding of the limitations of fertility and may lead to more people planning to have children during their most fertile years[27]. Furthermore, more awareness of the limitations of ART is needed to counteract media reports of celebrities having babies in their late 40's which can lead to the erroneous belief that ART can overcome age-related fertility decline[28].

Limitations

A limitation of this study was the disparity between the number of women in the donor group compared to the autologous group. In Australia and New Zealand, only altruistic gamete and embryo donation is permissible which contributes to the current shortage of oocyte donors. In addition, a small proportion of women (less than 2%), were counted in both the donor and autologous groups as they were treated with autologous oocytes before being treated with donor oocytes. While judged as unlikely due to the small numbers, this may have influenced the study findings. The lack of information available on clinic-specific protocols and processes for ART (such as the assessment of oocyte quality and ICSI timing) as these may potentially have an impact on clinical outcomes[29]. Further studies are required to evaluate the influence of these kinds of technical aspects on clinical outcomes. Demographic confounders, including

obesity and cigarette smoking, medical conditions and other residual confounders, which may have affected the findings of this study, are not recorded in the VARTA dataset.

In conclusion, this study shows that most women in their forties who access ART use their own oocytes despite the minimal chance of success. We found that, across all age groups, women ≥40 years using donor oocytes were five times more likely to have a live birth than women using autologous oocytes. These findings can be used when counselling women ≥40 years who contemplate using ART to conceive and help them make informed decisions about ART and whether to use their own or donor oocytes. The most important part of counselling is to inform women that the donor should ideally be <40 years or for an even better chance of success, younger than 35 years. The findings can also inform government policies and health promotion campaigns encouraging childbearing when the chance of spontaneous conception is greatest, thus reducing the personal and public cost of ART use.

References

1. Australian Bureau of Statistics. *Births, Australia 2017*. Canberra: Australian Bureau of Statistics, 2018.
2. Mills M, Rindfuss RR, McDonald P, te Velde E. Why do people postpone parenthood? Reasons and social policy incentives. *Hum Reprod Update* 2011; **17**:848-860.
3. Schmidt L, Sibitja T, Bentzen JG, Nyboe Andersen A. Demographic and medical consequences of the postponement of parenthood. *Hum Reprod Update* 2012; **18**:29–43.
4. te Velde, Habbema D, Leridon H, Eijkemans M. The effect of postponement of first motherhood on permanent involuntary childlessness and total fertility rate in six European countries since the 1970s. *Hum Reprod* 2012; **27**:1179–1183.
5. Hammarberg K, Kirkman M, Pritchard N, Hickey M, Peate M, McBain J, Agresta F, Bayly C, Fisher J. Reproductive experiences of women who cryopreserved oocytes for non-medical reasons. *Hum Reprod* 2017; **32**:575-581.
6. Soderstrom-Anttila V, Foudila T, Hovatta O. Oocyte donation in infertility treatment: a review. *Acta Obstet Gynecol Scand* 2001; **80**:191–199.
7. Newman JE, Fitzgerald O, Paul RC, Chambers GM. *Assisted reproductive technology in Australia and New Zealand 2017*. Sydney: National Perinatal Epidemiology and Statistics Unit, the University of New South Wales, 2019.
8. Daniluk J, Koert E, Cheung A. Childless women's knowledge of fertility and assisted reproduction: identifying the gaps. *Fertil Steril* 2012; **97**:420-6.
9. Meldrum DR. Preimplantation genetic screening is alive and very well. *Fertil Steril* 2013; **100**:593–4.
10. Savasi VM, Mandia L, Laoreti A, Cetin I. Maternal and fetal outcomes in oocyte donation pregnancies. *Hum Reprod* 2016; **22**:620–33.
11. Hammarberg K, Johnson, L. & Petrillio, T. Gamete and Embryo Donation and Surrogacy in Australia: The Social Context and Regulatory Framework. *Int J of Fertil and Steril* 2011; **4**:176-183.
12. Stern JE, Hickman TN, Kinzer D, Penzias AS, Ball GD, Gibbons WE. Can the Society for Assisted Reproductive Technology Clinic Outcome Reporting System (SART CORS) be used to accurately report clinic total reproductive potential (TRP)? *Fertil Steril* 2012; **97**:886-889.
13. Wilkinson J, Bhattacharya S, Duffy JMN, Kamath MS, Marjoribanks J, Repping S, Vail A, Wely M, Farquhar CM. Reproductive medicine: still more ART than science? *BJOG* 2019; **126**:138-141.
14. Wilkinson J, Roberts SA, Vail A. Developments in IVF warrant the adoption of new performance indicators for ART clinics, but do not justify the abandonment of patient-centred measures. *Hum Reprod* 2017; **32**:1159-59.
15. Maheshwari A, McLernon D, Bhattacharya S. Cumulative live birth rate: time for a consensus? *Hum Reprod* 2015; **30**:2703-2707.
16. Abdalla HI, Bhattacharya S, Khalaf Y. Is meaningful reporting of national IVF outcome data possible? *Hum Reprod* 2010; **25**:9–13.
17. Malizia BA, Hacker MR, Penzias A. Cumulative live-birth rates after in vitro fertilization. *N Engl J Med* 2009; **360**:236-243.

18. Chambers, G.M., Repon, P.C., Harris, K., Fitzgerald, O., Boothroyd, C.V., Rombauts, L., Chapman, M.G. & Jorm, L. Assisted reproductive technology in Australia and New Zealand: cumulative live birth rates as measure of success. *Med J Aust* 2017; **207**:114-118.
19. Bender, R. & Blettner, M. Calculating the "number needed to be exposed" with adjustment for confounding variables in epidemiological studies, *J Clin Epid* 2002; 55:525-530.
20. Hogan RG, Wang AY, Li Z, Hammarberg K, Johnson L, Mol BW, Sullivan EA. Oocyte donor age has a significant impact on oocyte recipients' cumulative live birth rate: a population-based cohort study. *Fertil Steril* 2019; **112**:724-30.
21. Chambers GM, Sullivan EA, Ishihara O, Chapman MG, Adamson GD. The economic impact of assisted reproductive technology: a review of selected developed countries. *Fertil Steril* 2009; **91**:2281–2294.
22. Connolly MP, Hoorens S, Chambers GM. The costs and consequences of assisted reproductive technology: an economic perspective. *Hum Reprod Update* 2010; **16**:603 – 613.
23. Commonwealth of Australia. *Donor practices in Australia*. Canberra: Department of the Senate, Parliament House, 2017.
24. National Health and Medical Research Council. *Ethical guidelines on the use of assisted reproductive technology in clinical practice and research*. Canberra: National Health and Medical Research Council, 2017.
25. Fertility Society of Australia. *Code of practice for assisted reproductive technology units.* Melbourne: Fertility Society of Australia, 2015.
26. Bunting, L., Tsibulsky, I. & Boivin, J. Fertility knowledge and beliefs about fertility treatment: findings from the International Fertility Decision-making Study. *Hum Reprod* 2012; **28**:385-97.
27. Hammarberg K, Setter T, Norman RJ, Holden C.A, Michelmore J, Johnson L. Knowledge about factors that influence fertility among Australians of reproductive age: a population-based survey. Fertil. Steril 2013; **99**:502–507.
28. Tremellen K, Savulescu J. Ovarian reserve screening: a scientific and ethical analysis. *Hum Reprod* 2014; **29**:2606-2614.
29. Rubino P, Vigano P, Luddi A, Piomboni P. The ICSI procedure from past to future: a systematic review of the more controversial aspects. *Hum Reprod Update* 2016; **22**:194–227.