

ART and the forgotten siblings:**a call for research****Running title:** Second child in ART

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Abstract

A broader definition of infertility is the incapacity to have the intended number of children. However, most literature on ART exclusively focuses on live birth as an outcome, rather than on the capacity to fully realize the reproductive wishes of the couples. This issue has probably received scant attention because the total fertility rate is below replacement levels in affluent countries, and one may simplistically assume that only a minority of couples may be interested in more than one child. This assumption, however, is unproven and presumably erroneous. Unfortunately, evidence on the rate of return in couples who conceived their first child with ART is scant and information on the intended number of children in infertile couples is lacking. In general, we plea for more research on this subject. The documentation of an intended number of children above two and a high return rate in infertile couples may lead to changes in clinical practice, such as the storage of oocytes or embryos prior to initiating embryo transfers. This could improve the chance of conceiving the second child when the couple comes back some years later. In addition, the identification of the determinants for non-return as well as those explaining the gap between the intended and the realized number of children may reveal specific barriers and possibly how to tackle them. However, at present, available evidence is insufficient to advocate any intervention. Thorough research is warranted.

Key words: infertility; assisted reproductive technologies; ART; intended children; family size; oocyte; embryo; aging.

AUTHOR: we can accept up to 10 key words, if adding more would be helpful.

Introduction

Infertility is defined as the incapacity to have a child or to achieve the intended number of children (WHO, 2018). However, most of the literature on ART focuses on live birth as an outcome for infertility, rather than on fulfilling the full reproductive wishes of treated couples. The proportion of women who achieve the intended number of children is a neglected concept in ART. This issue has probably received scant attention because the total fertility rate is below replacement levels in affluent countries (GBD 2019 Demographics Collaborators, 2020), and one may assume that only a minority of women may be interested in more than one child. However, this may not reflect the couples' real intentions. In most countries there is still a very strong two child norm (Albertini and Kohli, 2017; Beaujouan and Solaz, 2019).

Data on the intended number of children in the general population cannot be extrapolated to the subgroup of couples who are infertile. The two populations significantly differ. On one hand, one may hypothesize that couples embarking on ART are more committed to parenthood and could be more motivated than the general population to have more than one child. On the other hand, given the overwhelming emotional, financial, and logistic efforts associated with ART treatments, one may argue that couples who already had an ART-conceived child may revise their fertility intentions downward.

Obtaining information on the intended number of children in infertile couples is important because it may have practical consequences for everyday clinical practice.

The evidence on second child conception with ART

We failed to identify studies on the intended number of children in the infertile population but identified one contribution investigating the issue of the return rate for second ART-conceived

children (Paul *et al.*, 2020). Using the Australian and New Zealand Assisted Reproductive Database, Paul *et al.* (2020) identified 35,290 women who had a live birth with ART between 2009 and 2013, and evaluated whether they conceived a second ART live birth before December 2015. The overall return rate was 43%, and the cumulative rate at 6 years was 49%. Overall, one in two.

Even if informative, the study from Paul *et al.* (2020) is insufficient to draw a precise figure of the situation. There is no data on the comparator (the general population) and the study could not provide information on the reasons for non-return, such as the proportion of women conceiving other children naturally. Moreover, inferences of the situation observed in Australia (where inhabitants have a generous provision of ART services through the public health system) to the whole affluent world should be made with extreme caution (Adamson *et al.*, 2018). Obtaining evidence on the return rate from other countries is therefore warranted.

Implications for ART management

From a clinical perspective, improving our knowledge on the rate of return and its determinants may have repercussions on management. Indeed, considering the current trend of postponing first births in affluent countries, most women embark on ART when they are already in their late thirties (Mills *et al.*, 2011). When they will **return again** some years later for a second child, their probability of success will be significantly lower, the absolute rate of reduction of ART success being 2-4% per year (ACOG and ASRM; 2014; Somigliana *et al.*, 2020). Knowing in advance the number of intended children of the couple may influence the ART strategy. One may consider accumulating embryos (or oocytes) prior to initiating transfers, with the intent of having more efficient opportunities when the woman returns for the second child, two or more years later. Discussing with the couples the number of intended children prior to initiating ART is currently not recommended but may be important to

better plan the treatments. A shared decision-making process, focussing on the intended number of children rather than only on the first live birth, may influence the treatment strategy.

Such considerations could also be valid for elective egg freezing. Deciding in advance the appropriate number of oocytes to store (and therefore the number of required cycles) is challenging. However, there are now some tools published in the literature to counsel women based on age and oocytes retrieved (Goldman *et al.*, 2017; Cobo *et al.*, 2018). Conversely, there is no instrument that takes into consideration the number of intended children.

Implications for research

These clinical considerations remain theoretical and there is a fundamental need to obtain more precise and consistent information. For instance, the availability of robust data will allow us to precisely define the *incremental benefit* of a strategy of accumulation of oocytes/embryos.

To achieve this aim, there is not only the need to precisely assess the rate of return but also, most importantly, one should disentangle the determinants that predict this return. This may also reveal the sociologic, psychological, or financial barriers that do not enable couples to fully realize their reproductive plans and may reveal possible solutions. It could also allow the identification of subgroups of couples who may take advantage of a strategy of accumulation of oocytes/embryos. Moreover, one must define the proportion of women for whom the process of aging will hinder the chance of success with a new fresh cycle when she returns for the second child (the age at first conception and the interval between the children will inevitably be crucial factors). Finally, there is the need to obtain information on the emotional and psychological burden of an approach of repeated cycles prior to initiating the transfers. It has been shown that the emotional, psychological, physical, and economic burden of ART may be a barrier against this strategy of repeated stimulations (Gameiro *et al.*, 2012; Gameiro *et al.*, 2013). On the other hand, one may speculate that the availability of frozen

material may favour referral for a second child. Couples may be more prone to return if they do not have to re-initiate ovarian stimulation and oocyte retrieval (Vaughan *et al.*, 2017).

The intended number of children in infertile couples is another crucial point to clarify. This aspect differs from the rate of return, which may underestimate the real reproductive wishes of the couples. It is important to note that this issue poses some challenges. First, the intended number of children is not a stable concept as it may change over the lifespan. Data should not be collected exclusively at the time of ART initiation, when couples might have already revised their fertility intentions downwards. Instead, fertility intentions should also be assessed at other time points, such as after ART failures and soon after the first delivery. Second, one must consider that couples may break up. Intentions and fulfilments should be assessed separately for the two partners. Third, women and men who seek to form a family in different family structures (e.g. single, or in a same-sex or heterosexual partnership) may deserve independent evaluations.

Investigating the number of intended children also poses some strict methodological challenges. Ideally, one should collect information on both the intended number of children (how many children an individual plans to have; which is more likely to be subject to fluctuations based on the experience of infertility) and the desired number of children (how many children an individual wants, which is less likely to fluctuate as it is more a reflection of societal norms) (Bloom *et al.*, 2017). Moreover, one must collect data on other sociologic determinants of parenthood and ART utilization, such as financial situation, and the family and health situation. Clarifying these aspects may reveal the barriers hampering the full realization of their reproductive wishes, as well as possibly suggesting the means to tackle them.

Implications for trial reporting

Since the current main outcome for ART studies is the cumulative chance of live birth rather than the number of children, the possible detrimental effects of some interventions may not be evident. The pivotal randomized controlled trial (RCT) from Munné et al. on the role of preimplantation genetic testing for aneuploidy (PGT-A) well illustrates the relevance of this topic (Munné *et al.*, 2019). The PGT-A procedure caused the wastage of 40-50% of embryos potentially leading to live births (Paulson, 2019; Pagliardini *et al.*, 2020) but, surprisingly, the pregnancy rate per transfer was equivalent. Since the median number of available blastocysts was quite high (7.4 per group), the effects of this loss of healthy embryos were attenuated. Even if one in two euploid embryos was inappropriately discarded, there were remaining euploid embryos to transfer in most cases. The inopportune elimination of healthy embryos could become evident only once the woman returns for a second or third child. In line with these findings, a large retrospective study aimed at identifying factors associated with obtaining two or more children with one oocyte retrieval showed that performing PGT-A lowered this chance (adjusted odds ratio: 0.36, 95%CI: 0.21-0.62) (Vaughan *et al.*, 2017).

For this reason, we plea that information on residual embryos should be systematically reported in future trials. We obviously believe that the most suitable outcome would be the ultimate number of children but also recognize that this outcome is unrealistic in practice because of the need for several years for a definitive assessment. Data on residual embryos could be surrogate, but precious, information. Importantly, we scrutinized the five pivotal RCTs on ART published in the four major clinical journals of general medicine (*New England Journal of Medicine*, *Lancet*, *Journal of the American Medical Association* and *British Medical Journal*) during the last 4 years: two studies did not report the number of remnant embryos (Lensen *et al.*, 2019; Stormlund *et al.*, 2020), two studies reported it in the supplementary material (Wei *et al.*, 2019; Dang *et al.*, 2021) and only one study included this information in the main text of the manuscript (Yan *et al.*, 2021). None distinguished residual embryos according to whether the woman had had a live birth.

Conclusions

Physicians engaged in ART should consider enlarging the focus of their research and activity, shifting from the mere chance of live birth to the fulfilment of the intended number of children. Robust information on the predictive factors for returning for ART and on the gap between the intended and fulfilled reproductive plans is crucial and future studies on this topic are warranted. This information may allow us to disentangle the barriers between the intended and realized number of children and may reveal solutions to tackle this gap. It may also lead to changes in clinical practice such as the accumulation of oocytes and embryos prior to initiating the transfers.

Authors' roles

All authors participated to a preliminary in-depth discussion on the topic. E.S. wrote the first draft of the manuscript. All the other authors repeatedly revised the text.

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Conflict of interest

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