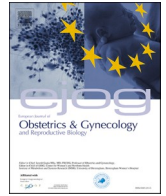




Contents lists available at ScienceDirect

# European Journal of Obstetrics & Gynecology and Reproductive Biology

journal homepage: [www.journals.elsevier.com/european-journal-of-obstetrics-and-gynecology-and-reproductive-biology](http://www.journals.elsevier.com/european-journal-of-obstetrics-and-gynecology-and-reproductive-biology)

Full length article

## The modest impact of assisted reproductive technology on the second birth: insights from a population-based study in Lombardy, Northern Italy

Giovanna Esposito<sup>a,\*</sup>, Paola Viganò<sup>b</sup>, Francesca Filippi<sup>b</sup>, Matteo Franchi<sup>c,d</sup>,  
Giovanni Corrao<sup>c,d</sup>, Fabio Parazzini<sup>a</sup>, Edgardo Somigliana<sup>a,b</sup>

<sup>a</sup> Department of Clinical Sciences and Community Health, University of Milan, Milan, Italy<sup>b</sup> Infertility Unit, Fondazione IRCCS Ca' Granda Ospedale Maggiore Policlinico, Milan, Italy<sup>c</sup> Unit of Biostatistics, Epidemiology and Public Health, Department of Statistics and Quantitative Methods, University of Milano-Bicocca, Milan, Italy<sup>d</sup> National Centre for Healthcare Research and Pharmacoepidemiology, Milan, Italy

## ARTICLE INFO

## Keywords:

Second birth  
Family rate  
Desired number of children  
ART  
IVF

## ABSTRACT

**Background:** In the field of assisted reproductive technology (ART), family rate is a neglected but emerging issue. The aim of the study was to investigate the epidemiological impact of ART on the second birth during the period 2007–2020 in Lombardy, Northern Italy.

**Methods:** We conducted a population-based study using administrative data from regional healthcare databases of Lombardy including first and second births occurred from 2007 to 2020. The proportion of deliveries after ART was calculated separately among first and second births. The probability of undergoing ART to achieve second birth compared to first one was estimated computing odds ratio (OR), crude and adjusted for maternal age, education, and nationality. We also assessed changes with age and calendar period.

**Results:** We obtained a cohort including 553,190 first births and 317,976 second births. The proportion of ART babies among first and second births was 4.3% and 1.0% respectively ( $p < 0.001$ ). The probability of undergoing ART to achieve second birth compared to first one, adjusted for age, education, and nationality, was 0.14 (95% CI: 0.13–0.15). The proportion of deliveries after ART increased with maternal age and along the calendar period but remained always markedly higher among first births rather than among second births.

**Conclusion:** ART played a significantly lower role in the determinism of the conception of a second birth in comparison to the conception of a first one.

## Introduction

Infertility is typically defined as a medical condition characterized by the inability of an individual or a couple to conceive a child or carry a pregnancy to full term after a year or more of regular, unprotected sexual intercourse. However, if the individual or couple is above the age of 35 years, the diagnosis may be made after only six months of unsuccessful attempts. Moreover, many couples may have fewer children than they would ideally like to have. Among other causes, this may be consequent to a delay in childbearing and secondary infertility [1]. In the field of assisted reproductive technology (ART), poor attention was given to the capacity to have the desired number of children [2], and most studies and registries simply reported on the cumulative live birth rate per couple [3–5]. The family rate, i.e., the capacity of a couple to achieve the number of desired children, may be a more complex but

appropriate outcome. Several years may be needed to obtain complete data on this outcome but information on this issue is warranted because it may influence also clinical strategies. For instance, if a 35 years old infertile woman desires two or more children, one could envisage to preliminary perform up to three retrieval cycles and store oocytes or embryos prior to initiate the transfers. This may overcome the well-known and rapid decline in in vitro fertilization (IVF) success after 35 years [6].

Information on the rate of infertile women who needed ART to conceive their first child and referred again to ART centres for other children is very limited [2]. Using the Australian and New Zealand Assisted Reproduction database, Paul et al. reported a 43% rate returning to treatment after an ART-conceived live birth. They also estimated that between 61% and 88% of them could achieve the second child [7]. We failed to identify additional studies on this topic.

\* Corresponding author at: University of Milan, via Celoria 22, Milan 20133, Italy.

E-mail address: [giovanna.esposito@unimi.it](mailto:giovanna.esposito@unimi.it) (G. Esposito).

<https://doi.org/10.1016/j.ejogrb.2023.06.027>

Received 23 April 2023; Received in revised form 20 June 2023; Accepted 26 June 2023

Available online 28 June 2023

0301-2115/© 2023 The Authors. Published by Elsevier B.V. This is an open access article under the CC BY license (<http://creativecommons.org/licenses/by/4.0/>).

To investigate the epidemiological impact of ART on the number of children, we evaluated the relative contribution of these techniques to first and second births during the period 2007–2020 in Lombardy, Northern Italy.

## Materials and methods

We conducted a population-based study of collected data regarding all deliveries that occurred in Lombardy during the period 2007–2020.

The regional healthcare utilization databases, in particular the hospital discharge forms [scheda di dimissione ospedaliera (SDO)] and the certificate of delivery assistance (CedAP) registry were used as data sources. The first reports, among other information, diagnoses and procedures of inpatients of public or private hospitals. The second is the main source for the collection of data related to the birth event; at delivery, midwives collect these data including parents' socio-demographic characteristics, previous obstetric history, current obstetric history, type of conception, mode of labour and delivery, gestational age at birth, neonatal characteristics, and outcomes. This study was conducted according to the guidelines laid down in the Declaration of Helsinki. As all these administrative data were handled anonymously, ethical approval is not required in Italy.

We identified all the deliveries recorded in Lombardy between 1st January 2007 and 31st December 2020 through the linkage of CedAP and SDO databases, including those of mothers aged 18 to 45 years old and those occurred between 22 and 42 weeks of gestation (we excluded women delivering after 42 weeks gestation because it could be a compilation error since in Lombardy full-term pregnancies are induced before 42nd week). Exclusion criteria were the following: (i) deliveries with missing or not clear information concerning the type of conception, (ii) deliveries with missing information concerning vitality of newborn, stillbirths, or neonatal deaths, and (iii) third (or higher birth order) deliveries or those with missing information concerning the birth order. We performed the cohort selection in September 2022.

The total number of first and second births was obtained. Descriptive statistics were used to summarize characteristics of women who delivered their first or second birth, such as age at birth, nationality, and educational level. Differences on the observed variables between the two groups were tested by using Chi-squared test.

The type of conception was our focus. The relative information was dichotomous, i.e., natural or through ART. Births achieved after ART were obtained with ovarian stimulation, intrauterine insemination (IUI), conventional IVF, or intracytoplasmic sperm injection (ICSI). The proportion of deliveries after ART was calculated separately in the two groups (i.e., first and second birth) according to maternal age at birth

and calendar period.

In Lombardy during the whole study period, there was no limitation on the number of cycles covered by the public health system. The decision on the appropriate number of cycles to be performed and age limitations were demanded to physicians who decided based on risks-benefits balance. There are also no limitations on the number of children that can be obtained with ART.

The odds ratio (OR) of ART use among second births compared to first births was estimated and further adjusted for maternal age, nationality, and educational level.

Two sub-analyses were performed. First, to exclude those cases who had a twin pregnancy at first delivery, we selected a sub-cohort of women who had a first singleton births from 2007 to 2017. Second, we selected a sub-cohort of women who had first birth after ART during the period between 2007 and 2017 to quantify how many couples conceived naturally a second birth after having had one successful ART.

All analyses were performed using the Statistical Analysis System Software (version 9.4; SAS Institute, Cary, NC, USA).

## Results

A total of 1,100,058 deliveries occurring in Lombardy from the 1st January 2007 to the 31st December 2020 were identified. We excluded (i) 4481 deliveries with missing or not clear information concerning the type of conception, (ii) 3453 deliveries with missing information concerning vitality of the newborn, stillbirths or neonatal deaths, and (iii) 220,958 deliveries of third (or higher birth order) children or with missing information concerning the birth order.

We obtained a final cohort of 871,166 deliveries. Overall, 553,190 were first births and 317,976 were second births. The baseline characteristics of the two groups are shown in Table 1. Significant differences emerged for age, nationality, and educational level. Mothers who had a second birth after ART were more common not Italian and less educated compared to those who had a first birth after ART.

Overall, 27,037 deliveries were obtained with ART (3.10%, 95%CI: 3.07–3.14%). They included 9901 IVF procedures, 10,672 ICSIs, 2280 IUIs, 1438 ovarian stimulations alone, and 2746 unspecified treatments. The number (proportion) of ART babies among first and second births was 23,989 (4.3%) and 3048 (1.0%), respectively ( $p < 0.001$ ). The probability of undergoing ART among second compared to first births was reduced (OR = 0.21, 95%CI: 0.20–0.22). When we adjusted for age, education, and nationality the OR was 0.14 (95%CI: 0.13–0.15).

The proportion of ART births among first and second births re-analysed according to maternal age is shown in Fig. 1. The relative percentage of births obtained with ART increased with age for both first

**Table 1**  
Maternal characteristics of women who delivered their first or second birth.

Maternal characteristics	First birth		Second birth	
	Natural N (%)	ART N (%)	Natural N (%)	ART N (%)
Age				
<30	211,022 (39.9)	1801 (7.5)	78,812 (25.0)	172 (5.6)
30–34	190,053 (35.9)	6653 (27.7)	115,142 (36.6)	657 (21.6)
35–39	104,401 (19.7)	9657 (40.3)	98,952 (31.4)	1406 (46.1)
≥40	23,725 (4.5)	5878 (24.5)	22,022 (7.0)	813 (26.7)
Citizenship				
Italian	409,827 (77.4)	21,109 (88.0)	229,672 (72.9)	2586 (84.8)
Not Italian	119,374 (22.6)	2880 (12.0)	85,256 (27.1)	462 (15.2)
Education <sup>a</sup>				
Middle school	113,682 (21.6)	3069 (12.8)	83,678 (26.7)	461 (15.1)
High school	237,343 (45.1)	9992 (41.7)	139,381 (44.4)	1292 (42.4)
University	175,581 (33.3)	10,908 (45.4)	90,604 (28.9)	1292 (42.4)

<sup>a</sup> The sum did not reach the total due to missing values.

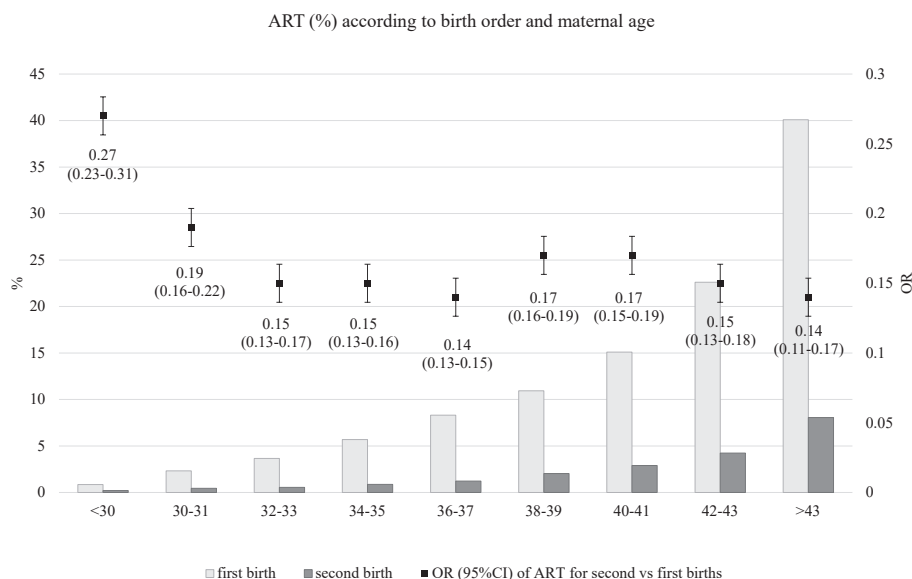


Fig. 1. The proportion of births after assisted reproductive technologies (ART) among first and second births according to maternal age groups.

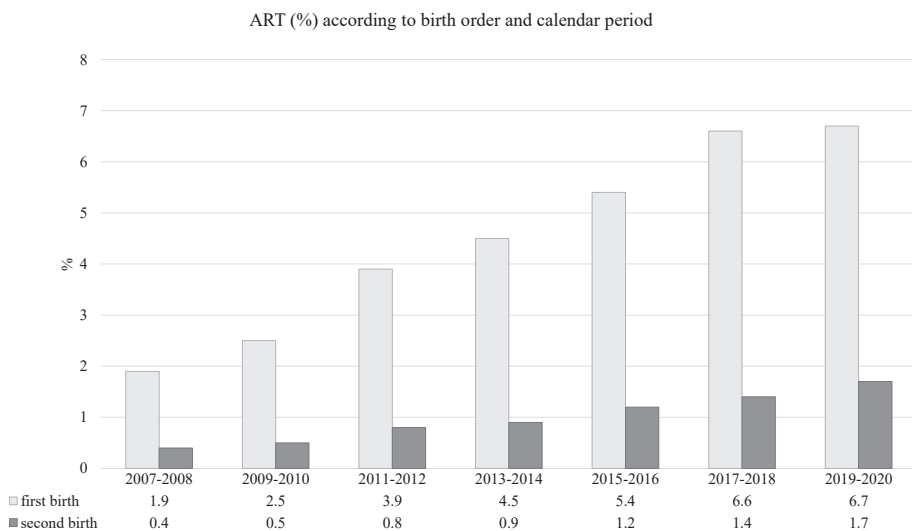


Fig. 2. The proportion of births after assisted reproductive technologies (ART) among first and second births according to calendar period.

and second birth. The probability of undergoing ART to achieve a second birth compared to first one was higher in younger mothers (OR = 0.27, 95%CI: 0.23–0.31 for women aged <30 years).

The proportion of ART among first and second births according to the different calendar periods is reported in Fig. 2. Over the period observed, ART rate increased for both first and second birth ( $p$  for trend < 0.001). However, the probability of undergoing ART to achieve a second birth compared to first one remained almost constant (data not shown).

In the sub-cohort including only women who had a first singleton birth between 2007 and 2017, the proportion of ART among first and second births was 3.1% and 1.1% respectively ( $p$  < 0.001). The probability of undergoing ART to achieve the second birth versus the first one was higher compared with that of the entire cohort (OR = 0.34, 95%CI: 0.33–0.36; adjusted OR = 0.23, 95%CI: 0.22–0.24).

Finally, when we considered only women who had a first ART birth between 2007 and 2017, the proportion of natural second births was 73.5% (versus 99.4% in the group of women who had a first natural birth in the same period).

## Discussion

In Lombardy, in the last fifteen years (2007–2020), ART played a significantly lower role in the determinism of the conception of a second birth in comparison to the role played for the conception of a first birth; among first births, the proportion of those conceived after ART was 4-fold higher when compared with second ones.

Our study design did not allow us to investigate the determinants of this finding. One could speculate several reasons. The most plausible is represented by the extreme stress caused by the inability to bear children and the concomitant anxiety and distress associated with ART programs, especially when expectations are violated by unsuccessful treatment cycles. The ART journey is very stressful and requires strong adherence and persistency to the programs; therefore, it is associated with a significant drop-out rate. According to several studies [8–12], the key reasons for discontinuing reproductive treatments, in absence of an active censoring by their physicians due to clinical reasons, are psychological burden and perception of a medical failure. One may hypothesize that this resilience is lower for second children. In the countries where a whole insurance coverage is not provided, the

financial burden could also play a role in the decision to interrupt the reproductive procedures. This cannot be an explanation in our context because the procedures were entirely covered by the public health system. On the other hand, one could argue that couples who succeed could be more motivated to parenthood than their fertile peers and wish to approach ART procedures again to have more children. A recent study [8] reported that having a good prognosis have a positive effect on the probability to return to ART, especially with increasing age. Our results argue against this view. The negative perceptions associated with the previous ART experiences may overcome the desire for a second child. To note, parenthood commonly arises from conflictual forces, and most births are not consciously planned. This uncertainty, typical of natural conceptions cannot be contemplated within the group of infertile couples requiring ART. We speculate that experiencing such difficult and painful programs could discourage a couple to return to fulfil their full reproductive wishes.

Alternative explanations deserve consideration. First, natural conceptions following a first ART baby could occur. Even if this factor cannot explain per se the markedly lower rate of second children obtained with ART, this possibility deserves consideration. The rate of women conceiving naturally after having a child with ART has been poorly investigated but it is presumably not negligible. According to our sub-analysis including only women who had a first birth with ART, a high proportion of natural second births emerged. Reasons cannot be explored but include the high frequency of subfertility rather than absolute sterility, the psychological benefit of being already parents, and pregnancy-related modifications of women genital tract that could somehow favour subsequent natural conceptions. Second, a lower rate of ART pregnancies may also reflect the relatively modest effectiveness of ART. A consistent proportion of women returning for ART fails and these women could not be captured with our study design. In other words, the lower rate of ART pregnancies among second births may not reflect a lower number of intended children. Finally, one must point out that, with the natural way, the completion of a second pregnancy is faster compared to ART and could be more satisfactory. One may hypothesise that, with the growth of the first child, the desire for second children progressively decreases.

Nowadays in most Western countries, the cultural frame, and the new role of women in the society modified the reproductive strategies adopted. Contextual and socioeconomic factors, i.e., financial constraints, competing educational, professional, and personal ambitions, delay the start of childbearing influencing indirectly the desired number of children and the actual family size. Maternal age at first birth plays a key role: postponing the transition to parenthood contributes significantly to the entity of the desired-actual fertility gap. Italy is one of the European countries with the highest discrepancy between desired and effective number of children; women aged 40 years or more, tend to close their reproductive window with 0.6 fewer children than the desired number, compared to 0.4 of the European average [13]. According to a study evaluating the timing of first pregnancy required to have a high chance to realize the desired family size, couples need to start the reproductive journey at age 31 years at the latest [1]. In our cohort we observed a decline in the ratio second to first birth after ART in women aged more than 40 years. This finding could reflect the decline in the probability of success of ART cycles among older women as we were not able to identify women who returned for a new ART program and failed. Shedding more light on this issue may be helpful in planning and adopting clinical strategies to overcome the rapid decline in ART success after 35 years. For instance, proposing more than one retrieval cycles and the storing of oocytes or embryos prior to initiate the transfers may represent an opportunity.

The desired number of children in the general population varies widely among subjects, from those do not wish to have more than one child to those aiming at 3–4 children. Among other factors, this may depend also on the potential capacity of the couple to reproduce, meaning if there are or not existent factors that can hinder an easy

conception or not. On this basis, we plea for general population education on this issue. One may even claim the spread of preconceptionally check-ups in younger ages [14]. This evaluation could inform couples regarding their capacity to reproduce. Fertility assessments are not highly reliable in predicting conception but could be sufficiently informative if properly interpreted. They may influence the reproductive plans of the couples (such as anticipating the initiation of natural pregnancy seeking or ART). At least, it could allow empowerment. This possibility is particularly relevant in European countries where women typically postpone their reproductive plans.

If in general Italian couples have fewer children than they would ideally like to have, it is also true that couples often adjust the desired number of children. For this reason, to justify the low impact of ART in the determinism of the conception of a second birth, one could also speculate that second children are less stringently desired and intra-couple conflicts may be more severe. Unconscious conceptions may be more frequent for second children. A recent survey in the United Kingdom showed that hesitant couples are common. Betweeners (those who already have child(ren) and want more in the future but are not actively trying to conceive) and flezers (those who may or may not already have and are unsure but or open to have child(ren) in the future) represent 11% and 28%, respectively [15]. These subjects are unlikely to undergo a new ART cycle to conceive but may have children if fertile. This possibility remains however speculative, infertile couples may differ from the general population for this aspect. Noteworthy, other complex sociologic, economical, and personal factors may influence the decision to embark for a second child. These variables may vary between ART and non-ART conceptions and cannot be disentangled from our study. Modality of delivery as well as obstetrics complications at the time of the first child may also have a role. In other words, the differences may not be exclusively related to ART-related direct burden.

To make this cohort representative of general population we decided to include in our cohort women aged from 18 to 45 years old. First, in Italy, it is not common that women under age of 18 years undergo ART. Second, the number of deliveries over 45 years is very low (0.3%). In addition, since our intent was to assess the impact of ART, we decided to exclude third (or higher order) births, because the proportion of ART births among these was <1%.

Some limitations of the current study should be considered. First, we were not able to establish for all mothers undergoing to ART procedures for the second birth if they achieved their first one after ART or natural conception. A study on the reproductive trajectories of all women would be required to address this aspect. This could be a valuable contribution to the field. However, in our setting, we lack information on women's history before 2007. Therefore, a study focussing on trajectories would need a marked reduction of the study period (and sample size). Second, it must be considered that in Lombardy there is no limitations on the number of cycles covered by the public health system. This is a situation that is uncommon in Western countries and could lead to overestimate the role of ART for second children compared to other contexts. The full financial coverage may indeed be considered a factor favouring ART uptake. On the contrary, favouring public policies to assist couples for a second child or more (such as bonuses) are in place in Italy but they are inadequate and cannot be expected to play a major role. Results could be partly different in countries with a more supportive welfare for families. In addition, we were not able to identify women who changed the partner between the first and second birth. This may have introduced a confounder, albeit with a plausible minor role in the explaining the markedly lower rate of ART use for a second birth. Finally, women who had twin pregnancies at first ART pregnancy may not seek for a second birth. This can lead to underestimate the possible role of ART. However, the observation that the contribution of ART for second births only mildly changed over time argue against this criticism. Indeed, the rate of twin pregnancy markedly shrank during the study period in our context [16–17]. If twin pregnancies at first delivery played a crucial role in explaining our findings, one had to expect a significant increase in the

role of ART for second children over the calendar period, but this did not occur. Our sub-group analysis excluding women who had a first twin pregnancy confirms this view.

Family size in ART is a neglected but emerging issue. Our study highlights a limited use of ART for the conception of a second pregnancy. This issue needs to be addressed more in-depth because it can hide surmountable barriers among infertile couples. Further efforts should aim at better assessing the impact of ART on the desired family size using different study designs, as well as disentangling the determinants.

### Declaration of Competing Interest

Edgardo Somigliana reports grants from Ferring, grants and personal fees from Merck-Serono, grants and personal fees from Theramex, personal fees from Gedeon-Richter, outside the submitted work. Giovanni Corrao received research support from the European Community (EC), the Italian Agency of Drugs (AIFA), and the Italian Ministry for University and Research (MIUR). He took part in a variety of projects that were funded by pharmaceutical companies (i.e., Novartis, GSK, Roche, AMGEN and BMS). He also received honoraria as a member of the advisory board to Roche. The other authors declare that they have no conflicts of interest to disclose.

### Funding

This work was supported by a research grant from the Italian Ministry of Education, University and Research ("PRIN" 2017, project 2017728JPK). The grant provides financial support for the analysis of data. Further, this study was also partially funded by Italian Minister of Health – Current Research IRCCS.

### References

- [1] Habbema JDF, Eijkemans MJC, Leridon H, te Velde ER. Realizing a desired family size: when should couples start? *Hum Reprod* 2015;30(9):2215–21.
- [2] Somigliana E, Parazzini F, Goisis A, Esposito G, Li Piani L, Filippi F, et al. ART and the forgotten siblings: a call for research. *Hum Reprod*. 2023.
- [3] Smith ADAC, Tilling K, Nelson SM, Lawlor DA. Live-Birth Rate Associated With Repeat In Vitro Fertilization Treatment Cycles. *Jama-J Am Med Assoc* 2015;314:2654–62.
- [4] Chambers GM, Dyer S, Zegers-Hochschild F, de Mouzon J, Ishihara O, Banker M, et al. International Committee for Monitoring Assisted Reproductive Technologies world report: assisted reproductive technology, 2014. *Human Reproduction*. 2021. 36. 2921-34.
- [5] Wyns C, De Geyter C, Calhaz-Jorge C, Kupka MS, Motrenko T, Smeenk J, et al. results generated from European registries by ESHRE. *Hum Reprod Open* 2017;2021:2021.
- [6] Somigliana E, Busnelli A, Vigano P, Vegetti W, Goisis A, Vercellini P. Is early initiation of infertility treatment justified in women over the age of 35 years? *Reprod Biomed Online* 2020;40(3):393–8.
- [7] Paul RC, Fitzgerald O, Lieberman D, Venetis C, Chambers GM. Cumulative live birth rates for women returning to ART treatment for a second ART-conceived child. *Hum Reprod* 2020;35:1432–40.
- [8] Bedrick BS, Anderson K, Broughton DE, Hamilton B, Jungheim ES. Factors associated with early in vitro fertilization treatment discontinuation. *Fertil Steril* 2019;112:105–11.
- [9] Gameiro S, Boivin J, Peronace L, Verhaak CM. Why do patients discontinue fertility treatment? A systematic review of reasons and predictors of discontinuation in fertility treatment. *Hum Reprod Update* 2012;18:652–69.
- [10] Olivius C, Friden B, Borg G, Bergh C. Why do couples discontinue in vitro fertilization treatment? A cohort study *Fertil Steril* 2004;81(2):258–61.
- [11] Soullier N, Bouyer J, Pouly J-L, Guibert J, de La Rochebrochard E. Effect of the woman's age on discontinuation of IVF treatment. *Reprod Biomed Online* 2011;22(5):496–500.
- [12] Van den Broeck U, Holvoet L, Enzlin P, Bakelants E, Demyttenaere K, D'Hooghe T. Reasons for Dropout in Infertility Treatment. *Gynecol Obstet Inves* 2009;68:58–64.
- [13] Testa MR. Family sizes in Europe: Evidence from the 2011 Eurobarometer survey. *European Demographic Research Paper N. 2*. Vienna Institute of Demography, Austrian Academy of Sciences. 2012.
- [14] Birch Petersen K, Hvidman HW, Sylvest R, Pinborg A, Larsen EC, Macklon KT, et al. Family intentions and personal considerations on postponing childbearing in childless cohabiting and single women aged 35–43 seeking fertility assessment and counselling. *Hum Reprod* 2015;30(11):2563–74.
- [15] Grace B, Shawe J, Johnson S, Usman NO, Stephenson J. The ABC of reproductive intentions: a mixed-methods study exploring the spectrum of attitudes towards family building. *Hum Reprod* 2022;37:988–96.
- [16] Galati G, Esposito G, Somigliana E, Muzii L, Franchi M, Corrao G, et al. Trends in the incidence of major birth defects after assisted reproductive technologies in Lombardy Region. *Northern Italy J Assist Reprod Genet* 2023;40(4):857–63.
- [17] Esposito G, Cipriani S, Noli S, Franchi M, Corrao G, Parazzini F, et al. The changing impact of assisted reproductive techniques on preterm birth during the period 2007–2020 in Lombardy, Northern Italy. *Eur J Obstet Gynecol Reprod Biol* 2022;278:51–6.