

## ORIGINAL RESEARCH ARTICLE

# Probability of second live birth after first natural and medically assisted reproduction-mediated live birth: A historical cohort study

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## Abstract

**Introduction:** Evidence on the role of medically assisted reproduction (MAR) in achieving the desired number of children is very limited. The aim of the current investigation was to assess the probability and the mode of conception of a second live birth according to the mode of conception of the first one.

**Material and methods:** This historical cohort study was based on administrative data from regional healthcare databases. Women hospitalized for childbirth in Lombardy between January 1, 2007 and December 31, 2017 were identified. The probability of a second live birth up to 2021 was estimated using the Kaplan–Meier method. We calculated this probability according to the mode of conception of the first birth, and the analysis was also performed in strata of maternal age at first birth. Cox proportional hazards models were fitted to estimate the hazard ratio (HR) and 95% confidence interval (CI) of the association between mode of conception at first live birth and the probability of having a second live birth. Mothers were right-censored if they moved out of the region, died, or did not have a second live birth by the end of follow-up.

**Results:** We identified 431 333 women who had their first live birth after a natural conception and 16 837 who had their first live birth after MAR. The probability of having a second live birth was 58.6% and 32.1%, respectively in the two groups (HR = 0.68, 95% CI: 0.66–0.70). Considering solely women who naturally conceived their first live birth, the probability to have a second child with MAR was 1.1% and to have a second child naturally 59.3%. The corresponding values were 11.5% and 25.2% in the group of women with a first MAR-mediated live birth.

**Conclusions:** In our cohort, one woman out of 10 having a first MAR-mediated live birth underwent MAR programs again. Considering women who had a first natural live birth, this proportion was drastically reduced. In the field of MAR, more attention should be given to the capacity of a couple to achieve the number of desired children.

**Abbreviations:** CedAP, certificate of delivery assistance (certificate di assistenza al parto) registry; MAR, medically-assisted reproduction; SDO, hospital discharge form (scheda di dimissione ospedaliera) registry.

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## KEYWORDS

desired number of children, family rate, medically assisted reproduction, second birth

## 1 | INTRODUCTION

Despite the widespread use of medically assisted reproduction (MAR), very little is known about how these procedures contribute to family size.<sup>1</sup>

Most couples desire more than one child to complete their family. In Italy, the actual number of children per couple does not reflect the intentions. Although fertility rate has been steadily declining since 2010 (being 1.30 in Italy in 2020),<sup>2</sup> the number of desired children of Italian couples remains at two.<sup>3,4</sup>

Delaying the first child plays a crucial role and changes the reproductive schedule. The desire to have children remains strong even after the age of 40, an age associated with substantial infertility rates. This may contribute to the growing rate of couples undergoing MAR.

Recent evidence suggests that women embarking in MAR are more often nulliparae, indicating that MAR mainly contributes to reduce childlessness by helping women to obtain their first child, rather than satisfying the desired family size.<sup>5</sup>

The role of MAR in fulfilling couples' reproductive intentions is a challenging issue to investigate. Several years may be needed to assess MAR contribution to achieve the desired number of children; the mean interval between first and second birth generally is around 2 to 3 years. For example, using the Australian and New Zealand assisted reproduction database, Paul et al. reported a 43% rate returning to treatment after a MAR-conceived live birth. One in four women who returned to MAR did so within 1 year, 79% within 2 years, and 95% within 3 years of the first birth.<sup>6</sup>

In the current investigation, we worked out on the regional healthcare databases of Lombardy, a large region located in Northern Italy with up to 10 million inhabitants, where MAR procedures are fully supported by the public health system for all women aged 46 years or less regardless of their obstetric or medical history.<sup>7</sup> Our aim was to assess the probability to have a second live birth according to the mode of conception of the first one, with a focus on the role of the use of MAR for the second births. The study does not report on all women referred for MAR for a second child (this information is not available for this analysis), but only on those who succeeded.

## 2 | MATERIAL AND METHODS

We conducted a historical cohort study using administrative data from the regional healthcare utilization databases of Lombardy, in Northern Italy. The first source of data was the certificate of delivery assistance (certificate di assistenza al parto [CedAP]) registry, which includes parents' sociodemographic characteristics, previous

### Key Message

Until now the main goal of medically assisted reproduction (MAR) programs has been the reduction of childlessness; more attention should be given to the contribution of MAR to the desired family size.

obstetric history, current obstetric history, type of conception, mode of labor and delivery, gestational age at birth, and neonatal characteristics and outcomes. The second source of data was the hospital discharge form (scheda di dimissione ospedaliera [SDO]), which reports detailed information about inpatient and their hospitalization in public or private hospitals (eg unique identification code, admission and discharge dates, main and secondary diagnoses, and procedures). Each woman was identified with an alphanumeric anonymised code, which was reported in all the databases and allowed the record linkage. For this type of study ethical approval is not required in Italy.

We identified all women hospitalized for delivery in Lombardy between January 1, 2007 and December 31, 2017 from CedAP and SDO databases. Inclusion criteria were as follows: (i) women aged 18 to 45 years old, (ii) women who delivered between 22 and 42 weeks of gestation, (iii) women for whom the newborn could be linked to the mother, (iv) women without missing or not clear information concerning the type of conception, (v) women who delivered live births, and (vi) women for whom the persistence in the health system or their death could be assessed. The cohort was selected in October 2022.

To assess if a second delivery occurred, we looked for second deliveries from January 1, 2008 to December 31, 2021 from CedAP and SDO databases. We did not consider additional births after the second one.

The mode of conception was categorized as natural and MAR-mediated, that is, obtained after ovarian stimulation, intrauterine insemination, conventional in vitro fertilization, or intracytoplasmic sperm injection (ICSI).

Descriptive statistics were used to summarize characteristics of women at the time of their first live birth, including age (i.e., <30, 30–34, 35–39, ≥40 years), nationality (i.e., Italian or not), and educational level (i.e., middle school or less, high school, university). Differences on the observed variables between women who had only one delivery and women who had a second delivery were tested using the chi-squared test.

The overall cumulative probability of a second live birth in women who had a first naturally conceived birth and in women who had a first MAR-mediated birth was estimated using the

Kaplan-Meier method. Cox proportional hazard models were fitted for estimating the hazard ratio (HR) and the corresponding 95% confidence interval (CI) of the association between the mode of conception of the first birth and the probability to have a second one. Models were adjusted for maternal age (in continuous years) and educational level (i.e., middle school or less, high school, university). These two factors, routinely collected at birth, influence both the access to MAR and the decision regarding family size.<sup>8</sup> The analyses were repeated according to the mode of conception of the second birth and stratified for maternal age (i.e., <35, ≥35 years).

Each woman accumulated person-years of follow-up from the first birth until the earliest of followings: date of the second birth, date up to which the mother was covered by the regional healthcare system, date of the death of the mother, and December 31, 2021. Mothers were considered right censored if they moved out of region, if they died, and if they did not have a second delivery by the time of the end of follow-up (December 31, 2021).

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

## 2.1 | Ethics statement

This study followed the principles of the Declaration of Helsinki. Data used in this study were anonymized before its use. According to Italian law, studies based entirely on registry data are exempt from IRB authorization and informed consent (General Authorization for the Processing of Personal Data for Scientific Research Purposes Issued by the Italian Privacy Authority on August 10, 2018; <https://www.garanteprivacy.it/web/guest/home/docweb/-/docweb-display/docweb/9124510>).

## 3 | RESULTS

A total of 473 908 women hospitalized for their first birth in Lombardy from the January 1, 2007 to December 31, 2017 were identified from the CedAP and SDO databases. Out of these, we excluded (Figure S1): (i) 4007 women aged less than 18 or more than 45, (ii) 2515 women who delivered before the 22nd or after the 42nd week of gestation, (iii) 7909 women for whom the newborn could not be linked to the mother, (iv) 2983 women with missing or not clear information concerning the type of conception, (v) 1576 stillbirths or neonatal deaths, and (vi) 6748 women for whom the date up to which they were covered by the regional healthcare system or their possible date of death were unknown. Overall, 431 333 natural births and 16 837 MAR-mediated births were available for the analysis.

In the group of women who had a first MAR-mediated birth, 4979 second births were identified. In the group of women who had first birth after a natural conception, 232 000 second births were identified. No trend in the overall proportions of second births appeared to be significant over the study period (data not shown).

The characteristics of mothers according to whether they had a second birth and the mode of the conception of the second birth are reported in Table 1. Considering the mothers who had the first naturally conceived birth, those who had a second birth were younger in the case of a second natural conception (mean age at first birth: 29.3 years) than in case of a second birth after MAR (mean age at first birth: 32.3 years) ( $p$ -value < 0.001). Women who had a successful MAR treatment for a second time had a mean age at first birth of 34.8 years and were younger in comparison with women who had only one MAR-mediated live birth (mean age at first birth: 36.9 years;  $p$ -value < 0.001), but older in comparison with women who had a second naturally conceived birth (mean age at first birth: 33.6 years  $p$ -value < 0.001). As regard educational level, regardless of the mode of first conception, women who had a second birth was more educated ( $p$ -value < 0.001), especially if they underwent MAR.

Figure 1 provides the overall probability to have a second birth according to the mode of conception of the first one. In the group of women who achieved their first birth after natural conception, the probability of a second birth was 58.6%. The corresponding value in women who conceived their first birth after MAR was 32.1% (HR = 0.68, 95% CI: 0.66–0.70). The median time to second birth was 3.2 and 2.8 years ( $p$ -value < 0.001) in women who conceived their first birth respectively naturally and after MAR.

Figure 2 shows the probability of a second birth according to the mode of conception of the first one. Among women who had first naturally conceived live birth, the probability to have a second live birth was 1.1% and 59.3%, respectively after MAR and natural conception. The respective values were 11.5% (HR = 15.12, 95% CI: 13.99–16.35) and 25.2% (HR = 0.52, 95% CI: 0.50–0.54) in women undergoing MAR to achieve their first live birth.

Compared to the group of women who had the first delivery after natural conception, for both subsets of age, the probability a natural second delivery was significantly reduced (HR = 0.58, 95% CI: 0.55–0.60 and HR = 0.62, 95% CI: 0.59–0.66, respectively for women aged less than 35 years and those aged 35 years or more) and the probability of a second birth after MAR was significantly increased (HR = 19.49, 95% CI: 17.66–21.50 and HR = 10.86, 95% CI: 9.70–12.15, respectively for women aged less than 35 years and those aged 35 years or more) in the group of women undergoing MAR to achieve their first birth (Figure 3).

Table 2 provides the HR and corresponding 95% CI of the association between the mode of conception of the first birth and the probability to have a second birth in the total series and in strata of maternal age at first one.

## 4 | DISCUSSION

In our cohort, the probability of a second birth after a first one obtained with MAR was about half of that observed in mothers who conceived their first one naturally, being approximately 30% and 60%, respectively. As for second live births achieved after MAR, one woman out of 10 having a first MAR-mediated live birth had a

TABLE 1 Characteristics of study participants according to mode of conception and number of births.

Maternal characteristics	First birth after natural conception			First birth after MAR		
	Women who have only one live birth	Women who have a second live birth		Women who have only one live birth	Women who have a second live birth	
		Natural conception	MAR		Natural conception	MAR
Maternal age						
<30	60 677 (35.1)	111 815 (64.7)	457 (0.3)	634 (49.6)	520 (40.7)	124 (9.7)
30–34	65 916 (42.6)	87 982 (56.9)	682 (0.4)	2736 (56.6)	1515 (31.3)	583 (12.1)
35–39	55 706 (66.6)	28 788 (33.9)	475 (0.6)	4968 (72.8)	1328 (19.5)	528 (7.7)
≥40	17 034 (90.4)	1696 (9.0)	105 (0.6)	3520 (90.2)	207 (5.3)	174 (4.5)
Mean (SD)	32.1 (5.3)	29.3 (4.7)	32.3 (4.8)	36.9 (4.4)	33.6 (4.0)	34.8 (4.0)
Nationality						
Italian	155 904 (46.7)	176 777 (52.9)	1492 (0.4)	10 516 (70.3)	3158 (21.1)	1283 (8.6)
Not Italian	43 429 (44.7)	53 504 (55.1)	227 (0.2)	1342 (71.4)	412 (21.9)	126 (6.7)
Educational level						
University	58 414 (43.0)	76 638 (56.4)	795 (0.6)	4963 (67.9)	1617 (22.1)	729 (10.0)
High school	93 871 (48.0)	100 859 (51.6)	675 (0.3)	5198 (72.0)	1478 (20.5)	548 (7.6)
Middle school or less	45 618 (46.8)	51 591 (52.9)	247 (0.3)	1685 (73.7)	470 (20.6)	131 (5.7)

Abbreviation: MAR, medically assisted reproduction.

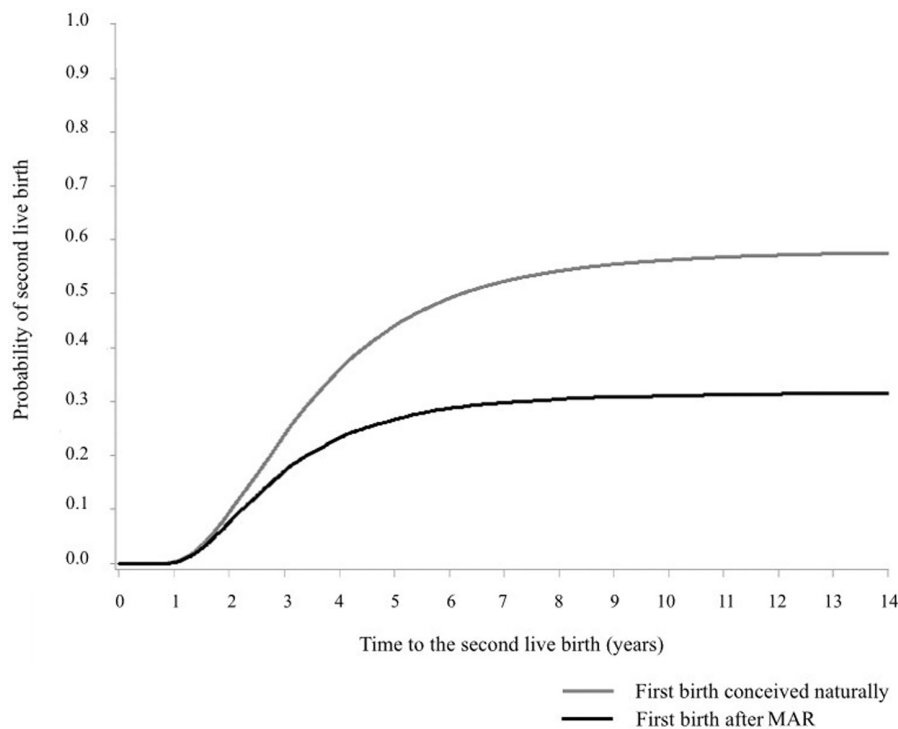


FIGURE 1 Probability of having a second live birth according to the modality of conception of the first. Italy, Lombardy, 2007–2021.

second birth by MAR. When we considered only women who had a first natural live birth, this proportion was drastically lower (about 1%).

In interpreting the results, it should be kept in mind that couples undergoing MAR for the first birth were not directly comparable with the fertile population, as they had, by definition, reduced fecundability. With this in mind, we could expect that the probability of having a

natural second birth was lower in infertile couples; thus, we focused on the mode of conception of second births according to the MAR use or not for the first birth. The chance of a second birth was higher among younger women at first one regardless the mode of conception. This latter finding is unsurprising: age is known as a major prognostic factor for the chance of natural conception as well as conception by infertility treatment. Further, this result is in line with previous evidence

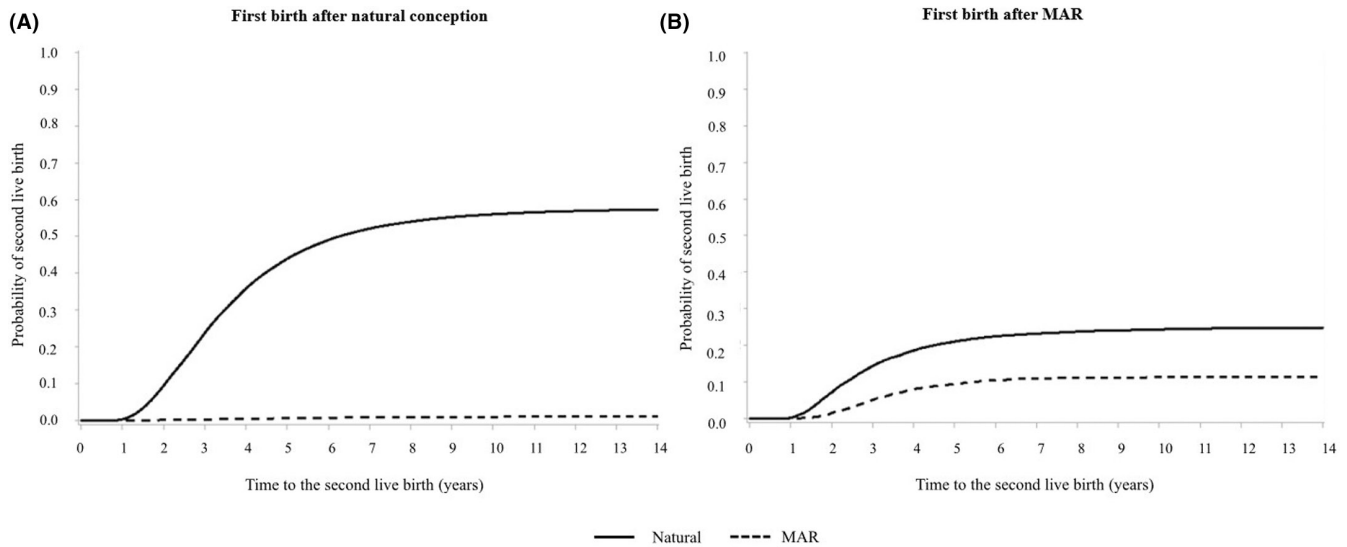


FIGURE 2 Probability of having a second live birth according to the modality of conception in women who achieved their first birth naturally (A) and in women undergoing medically assisted reproduction (MAR) to achieve first birth (B). Italy, Lombardy, 2007–2021.

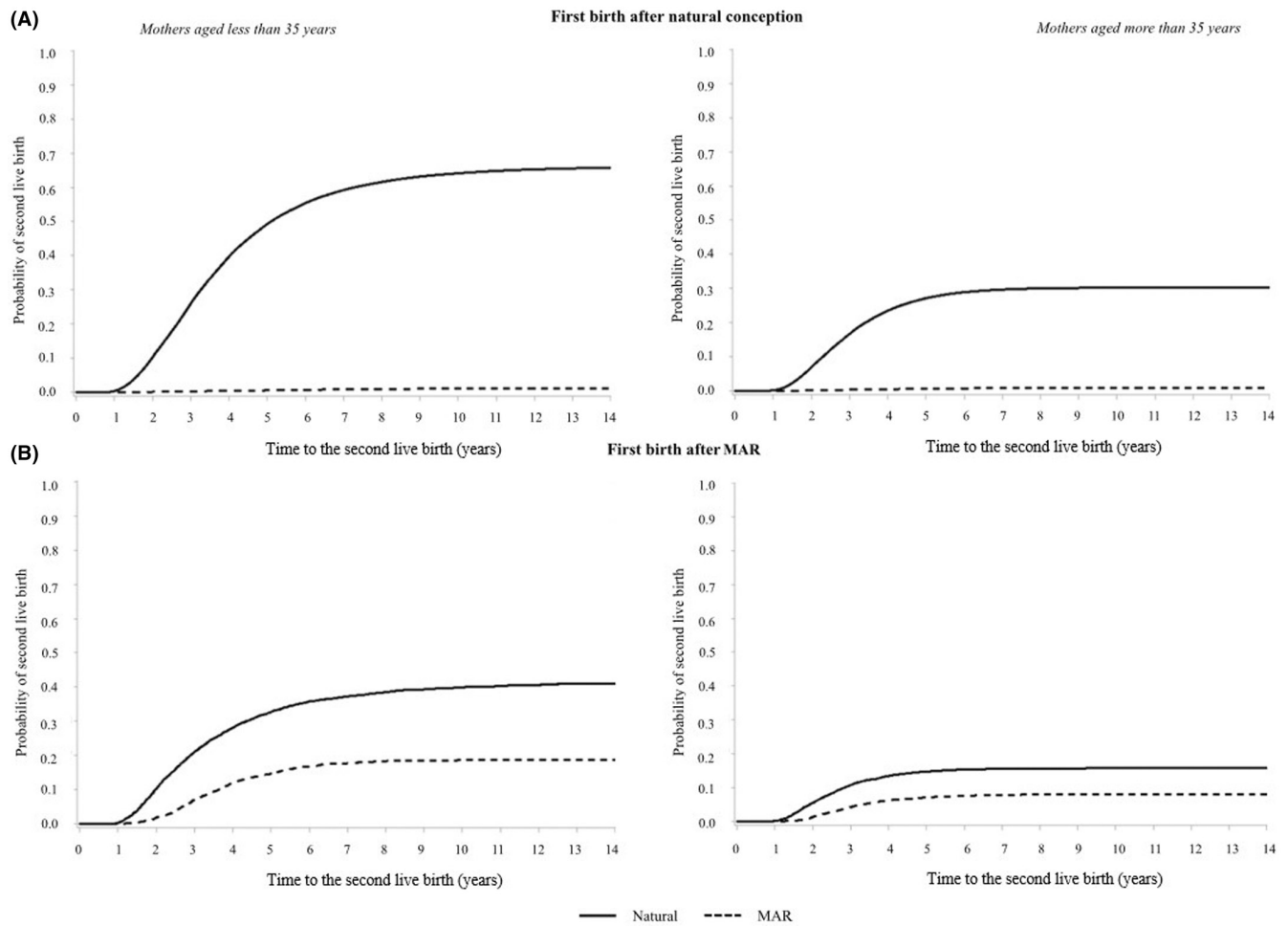


FIGURE 3 Probability of having a second live birth according to the modality of conception and maternal age in women who achieved their first birth naturally (A) and in women undergoing medically assisted reproduction (MAR) to achieve first birth (B). Italy, Lombardy, 2007–2021.

**TABLE 2** The hazard ratio (HR) and the corresponding 95% confidence interval (CI) of the association between the modality of conception of the first birth and the probability of having a second live birth, overall and in strata of maternal age at first birth. Italy, Lombardy, 2007–2021.

Modality of first conception	Total number of women		Overall second live birth		Second live birth after natural conception		Second live birth after MAR	
	N (%)	HR <sup>a</sup> (95% CI)	N (%)	HR <sup>a</sup> (95% CI)	N (%)	HR <sup>a</sup> (95% CI)	N (%)	HR <sup>a</sup> (95% CI)
Overall								
Natural	431 333		232 000 (53.8)	1 <sup>b</sup>	230 281 (53.4)	1 <sup>b</sup>	1719 (0.4)	1 <sup>b</sup>
MAR	16 837		4 979 (29.6)	0.68 (0.66–0.70)	3 570 (21.2)	0.52 (0.50–0.54)	1 409 (28.3)	15.12 (13.99–16.35)
<35 years								
Natural	327 529		200 936 (61.3)	1 <sup>b</sup>	199 797 (61.0)	1 <sup>b</sup>	1 139 (0.3)	1 <sup>b</sup>
MAR	6 112		2 742 (44.9)	0.84 (0.81–0.88)	2 035 (33.3)	0.58 (0.55–0.60)	707 (11.6)	19.49 (17.66–21.5)
≥35 years								
Natural	103 804		31 064 (29.9)	1 <sup>b</sup>	30 484 (29.4)	1 <sup>b</sup>	580 (0.5)	1 <sup>b</sup>
MAR	10 725		2 237 (20.9)	0.72 (0.69–0.74)	1 535 (14.3)	0.62 (0.59–0.66)	702 (6.6)	10.86 (9.70–12.15)

Abbreviations: CI, confidence interval; HR, hazard ratio; MAR, medically assisted reproduction.

<sup>a</sup>Estimated from Cox proportional hazards model including terms for maternal age at first delivery and educational level.

<sup>b</sup>Reference category.

reporting that the probability of a delivery following natural pregnancy after a first MAR birth decreases as the woman's age increases.<sup>9–12</sup> Maternal age, however, did not influence the chance of conception in a study investigating the occurrence of natural conception in patients who had discontinued unsuccessful ICSI treatment.<sup>13</sup>

In line with previous evidence,<sup>5,14</sup> in our cohort, MAR contributes in a limited way to satisfy the desired family size. Even in the group of women who had their first birth after MAR, conceptions of second births occurred more commonly naturally than through MAR.

Natural pregnancy after a first successful MAR attempt has been reported among about one in five couples, particularly for those who are younger, who have been infertile for a shorter period, and those with unexplained infertility.<sup>9,10,15</sup> For example, Hennelly et al. reported a natural conception rate of 20.7% within 2 years among couples who previously achieved a pregnancy through MAR (i.e., conventional in vitro fertilization or ICSI).<sup>9</sup> In such study, in the subset of women undergoing ICSI for a tubal factor or a severe male factor, a natural pregnancy rate of only 4.6% was found, meaning that the causes of subfertility are related with the chance of subsequent natural conception. According to Ludwig et al., 20.0% of the couples who tried to get pregnant again after a first child conceived by ICSI, conceived naturally at least once, with a delivery rate of 16.4%.<sup>10</sup> Further, in a large cohort of French couples undergoing MAR treatment, the rate of births following natural pregnancy was estimated to be 17% among successfully treated couples and 24% among unsuccessfully treated couples.<sup>15</sup> This high rate of natural conception after MAR attempts has been explained by the early use of MAR especially for cases of unexplained infertility and the positive placebo effect.<sup>16</sup> Natural pregnancies occurred after a successful MAR procedure or after adoption also suggests a relevant impact of the psychological sphere on fertility.<sup>17</sup>

In the interpretation of the high proportion of natural conception after MAR should be considered the fact that in Lombardy the access to MAR is not related to strict diagnostic criteria; thus, it is conceivable that also moderately subfertile couples may have access to MAR. Further, it should be considered that in some cases the second child is searched with another partner, thus affecting the mechanisms of couple infertility.

Reasons to explain the low rate of MAR use for the conception of the second child cannot be disentangled from our study. The observation that a consistent proportion of women conceived naturally can explain only part of this phenomenon. Indeed, this proportion is lower compared to the rate of natural second conceptions observed in fertile women, suggesting that a consistent proportion of women does not achieve the most common intended number of children (i.e., two). This may suggest an unmet need. We speculate that this may not be consequent to a specific choice of the infertile couples conceiving with MAR. First, couples facing and overcoming the difficulties of the MAR journey for the first conception may not be less interested to a second child compared to the general population. However, in our opinion, concerns against MAR, in terms of safety, logistic, emotional, and psychological burden, may play a crucial role. Infertile women

with one child may be less prone to re-undergo the overwhelming journey of MAR. This is probably true also for women who conceived naturally, as demonstrated by the extremely low proportion of MAR uptake in women who had a first natural conception. Only most motivated women with children could decide to embark in MAR treatments and this seems valid for both those who had a first MAR conception or a first natural conceptions. It is also unlikely that the lower number of second children could be due to a lower success rate of the procedure since a previous conception with MAR is a strong positive predictive factor for a new success.<sup>18</sup> Nevertheless, despite couples returning to MAR for a second birth would have a higher rate of success than couples undergoing their first attempt, the first success does not guarantee the success of later treatments and the live birth rates remain low at about 30%.<sup>19</sup> Moreover, we did not esteem financial reasons to play a major role since MAR is given for free by the public health system in the studied area.

Some limitations of the study should be recognized. First, we were unable to determine the proportion of women who underwent MAR and failed. The rate of MAR babies observed in our study is an under-estimation of the rate of MAR return. For this reason, it was not possible to infer the return rate of women undergoing MAR for a previous birth from our data, nor to evaluate the number of failed attempts in women who subsequently conceived naturally. This aspect deserves specific investigations with different study designs. In addition, we did not know if women changed the partner between the first and second child. This may have introduced a confounder, albeit with a plausible minor role in explaining the markedly lower rate of MAR second babies. The major strength of this study was its population-based design, which allowed for a large sample size with long-term follow-up and the use of hard variables routinely collected at birth. In addition, the results of the current study can be generalized to other high-income populations with similar MAR rates and public health coverage.

## 5 | CONCLUSION

Until now poor attention has been given to the contribution of MAR to the desired family size, the main goal remains to reduce childlessness. In our cohort, one woman out of 10 having a first MAR-mediated live birth had a second MAR baby and only one in a hundred if one considers women with a first naturally conceived birth. A lower return rate of couples is plausible to explain our findings but cannot be extrapolated from our data. Unsuccessful attempts are also likely to play a role, considering that couples have aged since their first success. However, other barriers to MAR access could play a role. Overall, disentangling the determinants of the low rate of second MAR babies is important if one aims at allowing infertile couples to fully accomplish their intended family size. Infertility treatment should go beyond only overcoming childlessness.

## AUTHOR CONTRIBUTIONS

All authors have contributed to and approved the final version of this manuscript. Term and conceptualization: FP and ES; Methodology, software, formal analysis, investigation, resources, data curation: GE and MF; Writing-original draft: GE and FP; Writing-review and editing: SC, FF, MF, ES, and PV; Supervision: GC, FP, and ES.

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## CONFLICT OF INTEREST STATEMENT

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.

## DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the Lombardy region, but restrictions apply to the availability of these data, which were used under license for the current study. The data used in this study cannot be made available in the manuscript, the supplemental files or in a public repository due to Italian data protection laws. The anonymized datasets generated during and/or analyzed during the current study can be provided on reasonable request, from the corresponding author, after written approval by the Lombardy region.

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### SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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