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# Determinants of the economic burden of ART on the Italian NHS: insights from the Lombardy region

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## Abstract

With the rising spread of Assisted Reproductive Technology (ART), it becomes imperative to understand the determinants of resource utilization in ART versus spontaneous pregnancies to enhance policies directed to pregnancy care. The focus of our study is to examine the costs associated with ART from the perspective of the Italian NHS and to investigate in depth the contributing social and clinical factors.

Using the healthcare informative system of Lombardy, a Region of Northern Italy, we gathered individual-level information for a cohort of women who experienced either spontaneous pregnancies or pregnancies following ART from 2007 until 2020. The information covered multiple healthcare services, and we used a propensity score matching technique to match couples of ART/No ART women based on a comprehensive set of confounders. We then applied statistical tests and regression models to identify the impact of ART on the reported cost differences.

Our cohort was composed of 44652 women and results revealed significantly higher costs for ART pregnancies, especially in terms of hospital admissions (additional 1611€, 95% CI 1558-1666) and drug prescriptions (additional 216 €, CI 95% 204-228) occurring before delivery. In-depth analysis showed for ART pregnancies, i) a higher likelihood of incurring expenses related to complications and ii) higher costs associated with two established clinical practices that lack scientific evidence supporting their efficacy.

Our study sheds light on the complex interplay of clinical and social factors influencing the ART burden, emphasizing the importance of tailored support and evidence-based practices in optimizing outcomes and resource allocation.

## Key points

• From the NHS perspective, ART pregnancies, compared to spontaneous pregnancies, mainly result in higher costs (especially in terms of hospital admissions and drug prescriptions occurring before delivery), even though they correspond to lower specialistic visits;

• The probability of spending for services related to complications is higher for ART pregnancies compared to spontaneous pregnancies, thus confirming the higher risk, regardless of single or twin pregnancy, of several obstetric and perinatal complications;

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• The higher costs in pregnancies following ART due to two consolidated clinical practices not supported by scientific evidence (aspirin and progestogen prescriptions) call for reflection on the unmet need of women experiencing ART in terms of emotional and psychological support.

**Keywords** Assisted reproductive technologies, ART, Healthcare costs, Economic burden, National healthcare system, Medically assisted reproduction

## Introduction

The latest world report developed by the International Committee for Monitoring Assisted Reproductive Technologies indicates that more than 1.9 million ART cycles are undertaken each year [13]. Following the international trend, also in Italy the utilization of these techniques has increased: the number of cycles per million of women in fertile age raised to 9077 in 2021, although with wide regional variations. Consequently, a total of 4.2% of national births are ART infants, which equals more than 15000 babies born in clinics performing ART [30, 42].

Within the extent of the growing body of research on ART, our interest has been to study the economic burden of ART on the National Health Service (NHS) and to detect its determinants, by exploring the cost implications of ART. Even though it has been showed that the cost to society for the coverage of ART treatments is relatively small, the NHSs require informative economic data supporting decisional processes, given their duty of allocating limited resources [10]. To this aim, our paper provides a complete picture of the economic resources invested by the NHS in ART pregnancies, with a comparison with spontaneous pregnancies. We then take a step further to support the design of health policies more aligned to the health needs, by focusing on understanding the determinants underneath the revealed costs. We refer to clinical and social determinants, capitalizing on two streams of knowledge. On one side, clinical literature has in fact reported higher risk for complications in ART pregnancies [3]; on the other side, recent works and anecdotical evidence narrate the social and emotional needs of women undertaking ART due to the burden of an often longer and more complex experience of conception [24].

For the mentioned purposes, our study delves into the sources of costs of ART by focusing on deliveries and the pregnancies leading up to those deliveries. We used the informative system of Lombardy, a Region of Northern Italy that accounts for 16.2% of the national centres performing 26% of the ART cycles each year [42]. By collecting information on different types of healthcare services provided to mothers such as drugs, specialist visits, access to emergency departments (ED), and hospital admissions, we tracked a multitude of sources of healthcare costs of a cohort of women that experienced either spontaneous pregnancies or pregnancies following ART.

Our ultimate aim is to disentangle the costs that are attributable to ART into 1) the costs due to clinical complications, and, if present, 2) the costs that refer to consolidated clinical practices not necessarily supported by scientific evidence that may be related to the unmet need of emotional and psychological support. In this way, through a snapshot of the resources invested in ART by the NHS, our results reveal the ART economic burden that is related to clinical determinants (1) or social determinants (2).

## Background

### Diffusion of ART

Assisted reproductive technologies (ART) have started to fill the debate on reproductive care since the birth of Louise Brown in 1978. During the last decades the utilization of these techniques has increased worldwide, with the number of cycles per million of women in fertile age increasing in Europe from 3503 in 2006 to 7794 in 2016. This increased demand has called for an increased attention in monitoring and reporting the healthcare services provided [54], together with the development of guidelines defined and agreed upon the complex combination of clinical work and laboratory procedures underlying ART [21]. Beyond the interest in these figures and outputs, researches have also deepened a number of issues related to the whole process of ART, which embraces a range of clinical, cultural, economic, social, psychological, and religious factors. Some, not exhaustive, examples of issues are represented by technological development and its efficacy, equity, accessibility, as well as ethical questions related for instance to cross-border dynamics [40], differences in legislative norms [32], heterologous fertilization, medical egg freezing [28], treatment discontinuation [8, 45] as well as the experience of unsuccessful ART cycles which do not lead to pregnancy but represent a relevant process both in terms of couples' experience and healthcare costs [9, 51].

As for the geographical context examined in our study, in 2021, there were 340 ART centers in Italy, with Lombardy having 55 centers, accounting for about 16% of the total. At the national level, overall about 86,000 couples

were treated, resulting in over 105,000 treatment cycles. These efforts resulted in over 23,000 pregnancies and over 15,000 documented births, contributing to 4.2% of all live births in the country. About half of the ART activity took place in the northern regions, with Lombardy alone accounting for about 24% of the total treatment cycles in Italy. When looking also at previous years, in Lombardy, between 2015 and 2021, about 19,000 couples were treated per year, with about 26,000 cycles initiated and 4,000 live births. Over the years, the most commonly used are the II-III level techniques, while I level ones, such as IUI, are becoming less common, dropping from about 3000 to 2000 cycles. Moreover, in 2021, 30% of I level cycles and 5% of II-III level cycles were performed in specialized private ART centers [30]. To the best of our knowledge, in Lombardy, there was no limit to the number of cycles covered by the public health system throughout the study period. The decision on the appropriate number of cycles and age limits was left to the physicians, who decided on the basis of the risk-benefit balance.

### ART and economic perspective

A first publication attempting to provide objective data to inform the policy discussion dates back to 1994 [34]. The complexity of ART is reflected also in the publications related to health economics issues [9, 20], which likewise need to consider multiple factors, such as the legislative framework, the availability of techniques, the affordability of treatment from a consumer and national perspective, and the underlying political and healthcare system [15]. A number of reviews have been conducted to generate supporting data for achieving consensus around the technique to be preferred and the numbers of embryos to be transferred [7, 12, 29, 48], knowing that "the main goal of ART should be the birth of a healthy child without excess problems during pregnancy, birth or childhood, rather than achieving as high a pregnancy rate as possible" [29]. The time window of this set of studies has been gradually extended from the moment of fertilization (with the ART direct costs) to the whole pregnancy, to the neonatal care of the new-born up to a children follow-up of 18 years (with the ART indirect costs) [6, 11, 14, 33, 49].

### ART and clinical factors

According to previous evidence produced within the clinical literature, a higher prevalence of several obstetric and perinatal complications that potentially could require hospitalization or the administration of drugs (e.g., unplanned peri-partum hysterectomy, intensive care unit admission, antepartum and postpartum haemorrhage, preterm premature rupture of membranes, pregnancy-induced hypertension) emerged among women undergoing ART when compared with those conceived spontaneously, regardless of single or twin pregnancy [3, 38].

### ART and social factors

The scientific literature has long studied the psychosocial stress in pregnancy, and has also documented the beneficial role played by social support, in terms of fewer mental health symptoms, reduced risk of preterm birth, and improved child development [26, 27, 36]. Social support may contribute to resiliency in pregnant women, buffering the impact of psychosocial stress risk factors on physical and mental health outcomes [2, 39]. In the same way, several studies have described the psychological and social support needed by couples undertaking ART cycles [1, 4, 24, 37, 41]. The path before the start of the pregnancy following ART is often longer and more complex than in spontaneous pregnancies, and this may further increase the psychological burden experienced by couples during pregnancy, notwithstanding the clinical conditions.

## Methods

### Data source

Our study made use of the regional healthcare information system of the Lombardy Region in Italy, which contains a variety of information about the healthcare services provided by the NHS to the ten million inhabitants of the region over the last few decades. As such, our data source does not include information neither on hospital admissions or outpatient visits occurred at private providers, nor on drugs of out-of-pocket purchase.

More specifically, our study is based on the data related to these types of NHS services: outpatient pharmaceutical prescriptions, specialistic visits and diagnostic examinations, access to Emergency Department (ED), and hospital admissions. The latest dataset to be published concerns admissions from the ED, for which data are available from 2010. The drug prescriptions are coded according to the Anatomical Therapeutic Chemical (ATC) classification system; the diagnoses and procedures of inpatient admissions and outpatient visits are coded according to the International Classification of Disease, Ninth Revision, Clinical Modification (ICD-9-CM) codes.

In particular, our study originated from the database reporting the Certificates of Delivery Assistance (i.e., the so-called CeDAP), which provides detailed clinical information on the current pregnancy and childbirth (e.g., type of pregnancy, mode of conception, labor, delivery, maternal and neonatal outcomes) and the previous obstetric history, together with information on mother's

personal characteristics (i.e., age and residency) and socio-economic traits of both parents (i.e., educational level and employment status).

As a unique personal identification code is used for all databases within the region, their record linkage allowed searching out the complete care pathway of beneficiaries of NHS. In order to preserve privacy, identification codes are automatically converted into anonymous codes, and the inverse process is prevented by deletion of the conversion table. In Italy, analyses of an anonymized administrative database in retrospective studies do not require Ethic Committee approval. All data were completely and permanently anonymized. All procedures were in accordance with the ethical standards of the institutional and national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

### Study design

Our study was a retrospective population-based cohort study. We selected all deliveries occurred in Lombardy Region between 1st January 2007 and 31st December 2020, according to following inclusion criteria: (i) deliveries which matched with a hospital ICD-9-CM or a Diagnosis Related Group (DRG) code related to childbirth from (ii) women aged 18 to 45 years, (iii) deliveries which reached 22 to 42 weeks of gestation, (iv) deliveries for which infants were paired to their mother, (v) deliveries without missing data on mode of conception, (vi) deliveries of women who were resident in Lombardy at least from the year before the pregnancy and for the entire year following the birth, (vii) deliveries associated to a hospital admission cost (i.e., excluding the ones erroneously corresponding to a null cost). Finally, we excluded second (or greater birth order) deliveries by using a set of variables contained within CEDAP, to whom we applied the restriction criteria of being either null or missing: the number of previous deliveries, the number of previous caesarian sections, the previous delivery date.

We defined the follow-up of each woman as starting at the conception (the date of conception was reconstructed from the date of birth and gestational week, both available within CEDAP) and ending one year after the delivery.

The time chart in Fig. 1 reports the study design just described, and also information on the variables' construction as will be explained in the following paragraphs.

### Baseline variables

To reach our first paper's contribution, i.e., to provide a complete picture of the economic resources invested by the NHS in ART pregnancies with a comparison with spontaneous pregnancies, the two cohorts have to be compared *exclusive of* pre-existing characteristics that make them differ in terms of healthcare expenditure. Indeed we know from the literature that access and use of healthcare services (and, thus, healthcare resources) may depend from personal characteristics that impact clinical needs, propensity for over/under treatment, ability to navigate the healthcare system, available networks of peers and/or healthcare professionals, and not ultimately economic constraints related to social inequalities. Some but not exhaustive examples are: patients with comorbidities are expected to use additional healthcare services related to their pathology; patients living in more urban contexts are surrounded by services closer and easier to be reached; migrant patients may face language barriers that reduce or delay the access to the NHS [46].

Overall, we identified a set of baseline variables that could be considered confounders when considering the costs of the medical services required: (i) maternal age, (ii) presence of comorbidity, investigated through the Multisource Comorbidity Score, i.e. a prognostic score which takes into account more than 30 chronic diseases/conditions, tracked by using hospital admissions

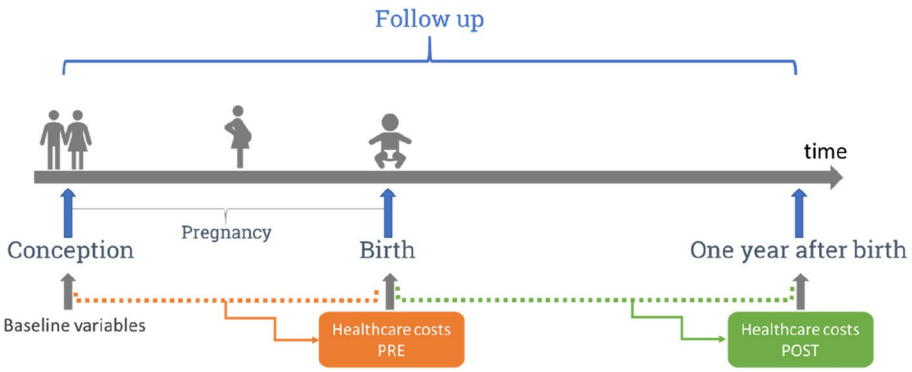


**Fig. 1** Time chart for the study design and variables' construction

and drug prescriptions [17], (iii) residency (whether in a province or not), (iv) nationality (i.e., Italian/not Italian), (v) type of pregnancy (i.e., singleton or multiple), (vi) education level of both parents (i.e., university, high school, middle or primary school), viii) employment condition of both parents (i.e., employed or unemployed), ix) marital status (i.e., married or not), x) multiple abortions (i.e., less or more than two), xi) healthcare costs during the year before conception (obtained considering any type of hospitalizations, pharmaceutical prescriptions, ED admissions, diagnostic examinations and outpatient visits).

All the variables were observed and measured before or at the start of the ongoing pregnancy (i.e., before the enrolment of the cohort), and were used in the process of matching, as explained in the respective section.

#### Exposure variable: ART conception

The exposure of interest of our analysis was the conception after ART. Information about the mode of conception (i.e., spontaneous or ART) was retrieved from the CeDAP database and we split the cohort into two groups according to this variable. For the sake of simplicity, in the following we refer to women that conceived after ART simply as "ART", while to women that conceived spontaneously as "No ART".

#### Dependent variables: healthcare costs

Our dependent variable was represented by a set of healthcare costs. To this aim, we collected data about the costs for the different NHS healthcare services referred to each woman during the follow-up. Table 1 reports a scheme of all the variables created, together with their definition, the specific diagnostic and therapeutic codes used, the healthcare service, and the time window to which they refer ("pre" if from the conception to the delivery; "post" if from the delivery to the year after). The variables are grouped into four categories, based on the criteria used to identify them.

Two categories of variables were built to depict the complete snapshot of resources invested in ART vs. spontaneous pregnancies: "General", including a set of dependent variables created by grouping all the individual expenses based on the healthcare service to which they were attributed, i.e., accesses to ED, pharmaceutical prescriptions, diagnostic examinations and specialistic visits, and hospital admissions (thus neither addressing specific medical or pharmaceutical treatment, nor specifically focusing at pregnancy); "Pregnancy", including a set of dependent variables that accounted for costs related to specific treatments attributable to pregnancy care.

The two categories that were built to answer our main research question on the determinants of ART burden are (1) "Complications": a set of dependent variables that referred to the costs due to clinical complications, such as the ones documented by the literature mentioned within the Background section [3, 38]; (2) "Practices": a set of dependent variables that referred to the costs related to consolidated clinical practices in pregnancies not necessarily supported by scientific evidence. As consolidated clinical practices, according to previous works [22, 50], we mainly referred to progestogen and cardioaspirin prescriptions, both of which own limited scientific evidence that supports their usage [43, 44]. In particular, currently there is no evidence in favour of a routine use of aspirin in order to improve pregnancy rates for a general population undergoing ART, its efficacy and safety are still debated [44]. As regard the progestogen, it is known for its use in the prevention of miscarriage, even if appropriateness in terms of efficacy has a long story of debate: first evidence suggesting no efficacy to prescribe progestogen for preventing miscarriages date back in 2003 [35]; a Cochrane review in 2013, updated in 2019, summarised that for women with unexplained recurrent miscarriages, supplementation with progestogen therapy may reduce the rate of miscarriage in subsequent pregnancies [25]; a randomized trial conducted in 2015 found no significant increase in the rate of live births even among women with a history of unexplained recurrent miscarriages [16]. Overall, latest guidelines concluded that evidence on the use of progesterone suggests no noticeable difference in live birth rates compared to placebo [43]. It should be mentioned that this drug, also for its name (progestogen comes from latin "pro-gestation") is widely known for its potential supportive role during pregnancy, also by the general population. Specifically referring to ART pregnancies, the use of progestogen in the luteal phase during assisted reproduction cycles is associated with higher rates of live birth or ongoing pregnancy than placebo [47]; however, there is no evidence about a prolonged use during pregnancy. For this reason, progestogen prescriptions have been accounted only after first pregnancy trimester [52].

#### Statistical analysis

We used a propensity score matching technique to match couples of women undergoing spontaneous vs. ART pregnancies, based on the set of independent variables described in the section related to baseline variables. The rationale behind the use of matching has been to compare women who started their pregnancy with equal levels of expected healthcare costs, apart from the cost attributable to any ART procedures. Building on the relevant size of our sample, the matching was 1:1 and the nearest neighbour technique, without a specific caliper size, was adopted in order to produce the covariate

**Table 1** Description of the variables referring to the healthcare costs tracked during the follow-up: type of healthcare service, time window considered, name, definition and diagnostic/therapeutic codes. Time window labelled as "pre" refers to the period from the conception to the delivery; "Post" refers to the period from the delivery to the year after. ATC: anatomical therapeutic chemical classification system. ED: emergency department. ICD-9-CM: international classification of Disease, Ninth Revision, clinical modification

| Category | Healthcare service | Time window (delivery) | Name | Definition | Diagnostic and therapeutic codes |
|---|---|---|---|---|---|
| General | Specialistic services | Pre | General_visits_pre | Total cost of all outpatient visits during pregnancy | All codes |
| | | Post | General_visits_post | Total cost of all outpatient visits after delivery | All codes |
| | Pharmaceutical prescriptions | Pre | General_drugs_pre | Total cost of all drugs prescribed during pregnancy | All codes |
| | | Post | General_drugs_post | Total cost of all drugs prescribed used after delivery | All codes |
| | Hospital admissions | Pre | General_hospital_pre | Total cost of all hospital admissions experienced during pregnancy | All codes |
| | | Post | General_hospital_post | Total cost of all hospital admissions experienced after delivery | All codes |
| | ED admissions | Pre | General_ED_pre | Total cost of all ED admissions experience during pregnancy | All codes |
| | | Post | General_ED_post | Total cost of all ED admissions experiences after delivery | All codes |
| Pregnancy | Specialistic services | Pre | Pregnancy_visits_pre | Total cost of outpatient visits related to pregnancy (e.g., amniocentesis, obstetric ultrasound, prenatal training, etc.) | ICD-9-CM codes: 75.10.1, 75.10.2, 75.10.3, 75.33.1, 75.34.1, 88.78, 88.75.2, 89.26.4, 93.37 |
| | | Post | Pregnancy_visits_post | Total cost of outpatient visits related to the post-partum state (i.e., gynecological visits) | ICD-9-CM codes: 88.78.2, 88.79.7, 89.26.1, 89.26.2 |
| | Pharmaceutical prescriptions | Pre | Pregnancy_drugs_pre | Total cost of acid folic prescriptions during pregnancy | ATC codes: B03BB |
| | Hospital admissions | Post | Pregnancy_hospital_post | Total cost of the hospital admission related to the delivery | ICD-9-CM diagnostic codes: V27, 640.–676., ICD-9-CM procedures codes: 72., 732.,735.,736., 738.–742., 744., 749.9 DRG codes: 370–375 |

**Table 1** (continued)

| Category | Healthcare service | Time window (delivery) | Name | Definition | Diagnostic and therapeutic codes |
|---|---|---|---|---|---|
| Complications | Hospital admissions | Pre | Complications_hospital_pre | Total cost of the hospital admission for complications related to pregnancy (e.g., antepartum haemorrhage, hypertension disorders, gestation diabetes, etc.) | ICD-9-CM diagnostic codes: 640.–649. |
| | | Post | Complications_hospital_post | Total cost of the hospital admission for complications related to post-partum state (e.g., major puerperal infection, complications of venous thromboembolism, etc.) | ICD-9-CM diagnostic codes: 670.–677. |
| | Specialistic services | Post | Complications_visits_post | Total cost of outpatient visits related to complications of the post-partum state (e.g., other dilation or curettage of the uterus, etc.) | ICD-9-CM codes: 75.8, 68.12.1, 69.09 |
| | Pharmaceutical prescriptions | Pre | Complications_drugs_diabetes_pre | Total cost of antidiabetic drugs prescribed during pregnancy | ATC codes: A10 |
| | | | Complications_drugs_hypertension_pre | Total cost of antihypertensive drugs prescribed during pregnancy | ATC codes: C02 |
| | | | Complications_drugs_heparin_pre | Total cost of heparin drugs prescribed during pregnancy | ATC codes: B01 |
| | | | Complications_drugs_antibiotics_pre | Total cost of antibiotics drugs prescribed during pregnancy | ATC codes: J01 |
| | | Post | Complications_drugs_hypertension_post | Total cost of antihypertensive drugs prescribed after delivery | ATC codes: C02 |
| | | | Complications_drugs_heparin_post | Total cost of heparin drugs prescribed after delivery | ATC codes: B01 |
| | | | Complications_drugs_antibiotics_post | Total cost of antibiotics drugs prescribed after delivery | ATC codes: J01 |
| Practices | Pharmaceutical prescriptions | Pre | Practices_progestogen_pre | Total cost of progestogen prescribed after the third month of pregnancy | ATC codes: G03D |
| | | | Practices_cardioaspirin_pre | Total cost of cardioaspirin prescribed before delivery | ATC codes: B01AC06, B01AC56 |

balance, that was, for the distributions of covariates in the two groups to be approximately equal to each other. We excluded cases having at least one covariate assuming missing mode to be able to perform the matching on all the set of baseline variables. To check for the quality of the propensity score matching, we performed a set of descriptive statistics related to the baseline variables as for the ART and No ART subgroups, and we compared the existing differences before and after the matching, using the t-test for continuous variables and the chi-square test for dichotomous variables. We made further matching attempts by increasing the ratio to 2:1 and setting a caliper size, but no relevant benefit has emerged in terms of post-matching results. Further information is available upon request.

Once identified our cohort of matched pairs, we investigated the differences in costs between ART and No ART for each source of cost. As for the methodology, we distinguished between the costs of type "General" and "Pregnancy", and the costs of type "Complications" and "Practices". The rationale behind this division was related to the low occurrence of the episodes tracked within the cost variables of "Complications" and "Practices" (statistics are reported in the Section "Descriptives of costs before matching" Appendix), which make less interpretable statistics such as means. For this reason, we treated the cost variables of type "General" and "Pregnancy" as continuous variables, while we transformed the cost variables of type "Complications" and "Practices" as dichotomous variables, with value 1 if costs were greater than zero, 0 otherwise.

We then calculated the differences in the average cost for type "General" and "Pregnancy", and the percentage of women having costs greater than zero for the type "Complications" and "Practices". We checked the statistical difference between the groups of ART and No ART by using the Wilcoxon-test for continuous variables, the chi-square test for dichotomous variables and outlined graphically the results.

We ultimately ran regression models: we performed one regression per each cost variable considering only the ART independent variable, to draw overall results about the positive/negative impact of ART on the source of cost. Linear regressions were run for continuous variables (type "General" and "Pregnancy"), logistic regressions were run for dichotomous variables (type "Complications" and "Practices"). Coefficients were reported along with 95% confidence intervals (CI). In case of linear regressions, coefficients can be interpreted as the amount of greater/lower cost that the NHS bears for women with ART pregnancy compared to the baseline cost borne for spontaneous pregnancy. In case of logistics regressions, exponentiated coefficients can be interpreted as the odds for the NHS of facing that cost for each woman with ART pregnancy vs. spontaneous pregnancy. We then ran the same regressions adding the interaction terms between ART and the years, to investigate if there were time trends for the costs considered. As a sensitivity analysis, we also repeated the regressions for continuous variables using GLM with gamma distribution to check for potential bias due to the skewed distribution of costs, but results were not reported since were very similar to the linear regression ones.

All datasets were built with SAS Studio 3.8 and analyses were performed with R version 4.3.0.

## Results

Figure 2 describes the procedure that drove to the final cohort. Our initial sample was composed by 1,130,599 deliveries, which were reduced to 539,303 after applying the inclusion/exclusion criteria. Of them, 516,182 (95.7%) were of women who conceived spontaneously and 23,121 (4.3%) of women who conceived after an ART treatment.

Before the matching process, it is interesting to map the frequency and average costs of spontaneous and ART pregnancies. Figure 3 reports the number of deliveries from 2007 to 2020. The different y-axis scales allow to highlight the opposite time trends of spontaneous deliveries vs. deliveries from ART.

Figure 4 reports the average "General" costs per woman related to the period before and after the delivery together with the cost of delivery, divided by year, calculated before the matching process. The graphs help to identify the existence of differences among the groups, which need to be further investigated. Additional statistics of all the cost variables considered in the study can be found in the Section "Descriptives of costs before matching" Appendix.

After having excluded the cases that had missing values for any of the baseline variables, and having performed the matching process, our cohort was composed of 44,652 women, 22,326 ART and 22,326 No ART.

Table 2 reports the main characteristics of the two groups of the cohort, i.e., ART vs. No ART, before and after the matching procedure. While before matching there were significant differences for all the independent variables in the two groups (as an example: the maternal age was 35.1 for ART pregnancies, 29.7 for the no ART pregnancies), after the matching progress the majority of variables assumed values not anymore significantly different in the two groups, or, if still different, appeared with mean/percentage values much closer than before. It should be noticed that the great difference observed in the mean previous healthcare costs (4447€ for ART pregnancies and 3548€ for No ART pregnancies) could be mainly attributed to the

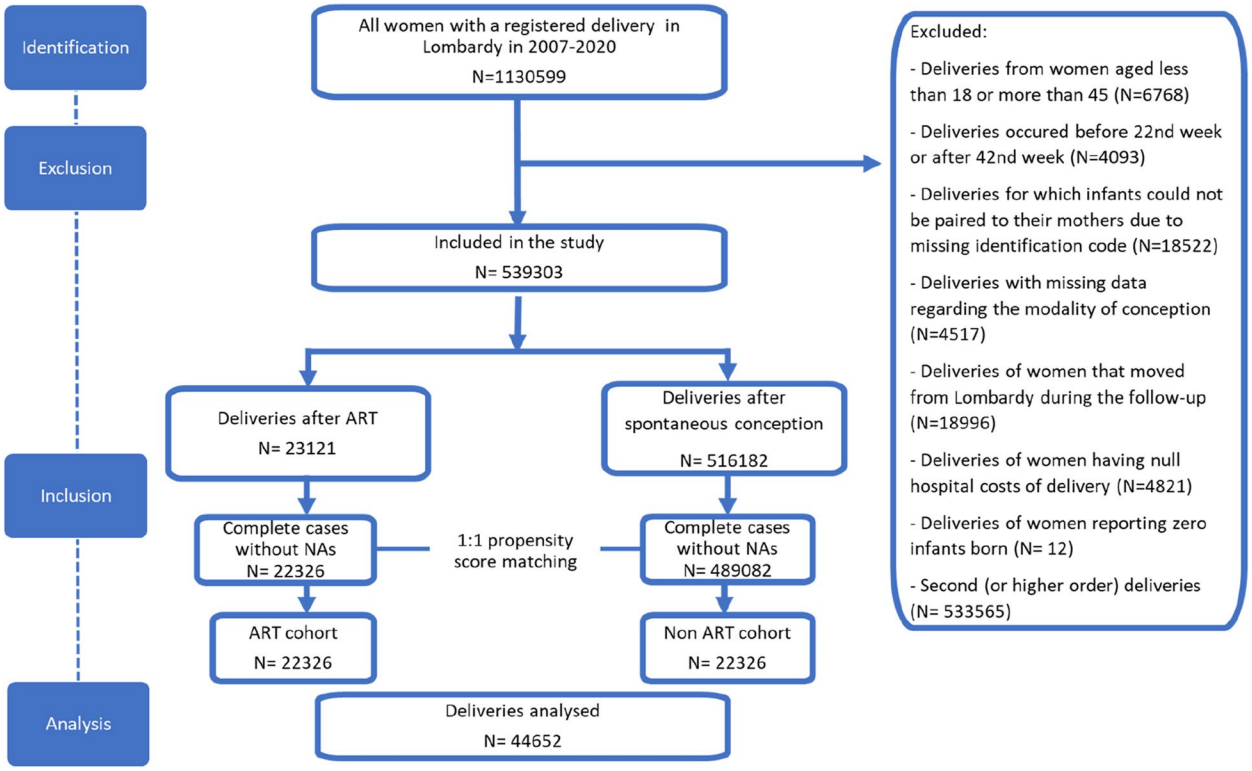


**Fig. 2** Flow chart of the cohort study

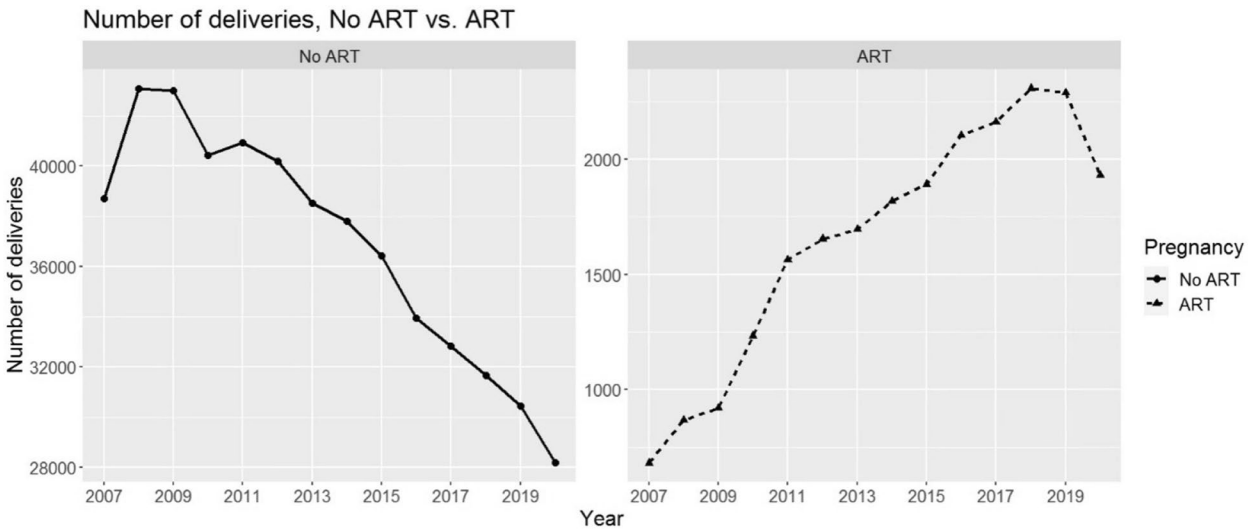


**Fig. 3** Number of deliveries according to the mode of conception during the time period considered

healthcare costs sustained in preparation for the beginning of the ART treatment, such as diagnostic exams or pharmacological prescriptions. An in-depth analysis on this aspect revealed that the median expense for ART-specific treatments in our cohort (e.g., sperm capacitation, ultrasound-guided needle aspiration of follicles, artificial insemination, gonadotropins, etc.) is 1748€ for the ART group, while it is zero for the No ART group.

Table 3 report the results from the regressions performed (i.e., intercept and coefficient for the covariate ART), divided into linear regressions for cost variables of type "General" and "Pregnancy", and logistic regressions

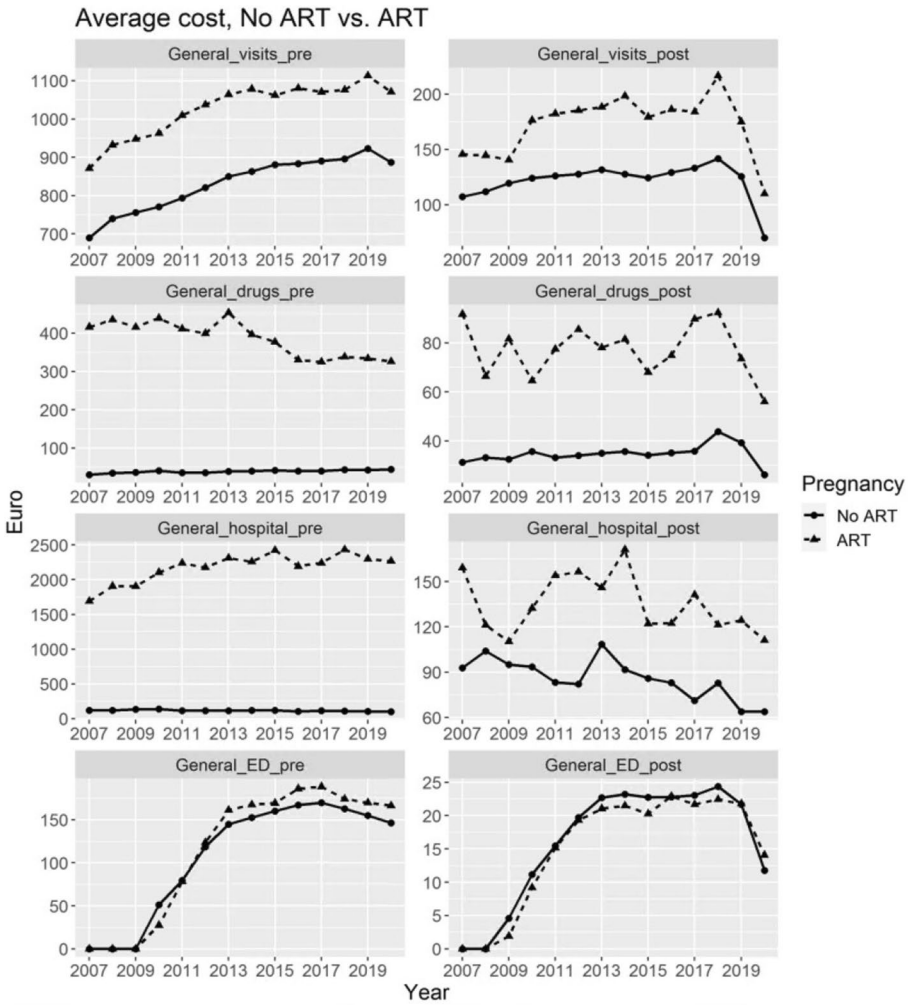


**Fig. 4** Average costs (€) per woman according to different cost variables, before matching

**Table 2** Characteristics of the cohort of ART and no ART deliveries before and after matching

| | | Pre matching | | | Post matching | | |
|---|---|---|---|---|---|---|---|
| | | **ART** ***n*** **= 22,326** | **No ART** ***n*** **= 489,082** | ***p*-value** | **ART** ***n*** **= 22,326** | **No ART** ***n*** **= 22,326** | ***p*-value** |
| Age (mean) | | 35.1 | 29.7 | < 0.001 | 35.1 | 35.1 | 0.03 |
| Municipality of residence | MI | 17% | 12% | < 0.001 | 17% | 17% | 0.5 |
| | Provinces | 8% | 8% | | 8% | 8% | |
| | Other | 75% | 80% | | 75% | 75% | |
| Civil status: married | | 76% | 61% | < 0.001 | 76% | 78% | < 0.001 |
| Education level mother: degree | | 45% | 34% | < 0.001 | 45% | 45% | 0.46 |
| Education level father: degree | | 33% | 23% | < 0.001 | 33% | 32% | 0.02 |
| Empolyment status mother: employed | | 85% | 75% | < 0.001 | 85% | 85% | 0.39 |
| Employment status father: employed | | 98% | 96% | < 0.001 | 98% | 98% | 0.44 |
| Nationality: Italian | | 88% | 79% | < 0.001 | 88% | 88% | 0.39 |
| Type of pregnancy: multiple | | 17% | 1% | < 0.001 | 17% | 17% | 0.05 |
| Multiple abortions: more than two | | 7% | 3% | < 0.001 | 7% | 9% | < 0.001 |
| Previous healthcare costs (mean) | | 4447€ | 514€ | < 0.001 | 4447€ | 3548€ | < 0.001 |
| Multicomorbidity score: greater than 1 | | 29% | 16% | < 0.001 | 29% | 32% | < 0.001 |

**Table 3** Results from regressions

| Type | Name | Linear regression | |
|---|---|---|---|
| | | **ART coefficients (95% CI)** | **Intercept (95% CI)** |
| General | General_visits_pre | −53.86 (−65.70, −42.04) | 1102.77 (1094.24, 1111.38) |
| | General_visits_post | −10.85 (−19.23, −2.50) | 188.51 (182.55, 194.73) |
| | General_drugs_pre | 215.88 (204.49, 227.59) | 159.19 (154.76, 163.78) |
| | General_drugs_post | −6.09 (−12.74, 0.52) | 83.84 (879.18, 88.88) |
| | General_hospital_pre | 1611.41 (1558.25, 1666.04) | 624.34 (610.08, 639.05) |
| | General_hospital_post | 8.90 (−7.34, 25.27) | 126.64 (116.18, 138.39) |
| | General_ED_pre | 7.45 (3.80, 11.11) | 130.83 (128.36, 133.38) |
| | General_ED_post | −1.59 (−3.61, 0.41) | 19.30 (17.90, 20.85) |
| Pregnancy | Pregnancy_visits_pre | −26.45 (−32.76, −20.14) | 436.77 (432.20, 441.41) |
| | Pregnancy_visits_post | 1.12 (0.59, 1.66) | 12.17 (11.82, 12.54) |
| | Pregnancy_drugs_pre | 0.81 (0.62,0.99) | 4.42 (4.30, 4.54) |
| | Pregnancy_hospital | 26.91 (12.44, 41.38) | 2241.64 (2231.50, 2251.83) |
| **Type** | **Name** | **Logistic regression** | |
| | | **ART coefficients (95% CI)** | **Intercept (95% CI)** |
| Complications | Complications_hospital_pre | 0.11 (0.05, 0.18) | −2.39 (−2.43, −2.34) |
| | Complications_hospital_post | 0.08 (−0.48, 0.64) | −6.84 (−7.27, −6.47) |
| | Complications_visits_post | 0.56 (0.21, 0.92) | −6.15 (−6.44, −5.88) |
| | Complications_drugs_diabetes_pre | −0.25 (−0.38, −0.12) | −3.72 (−3.81, −3.64) |
| | Complications_drugs_hypertension_pre | −0.01 (−0.26, 0.23) | −5.13 (−5.31, −4.97) |
| | Complications_drugs_heparin_pre | 0.88 (0.81, 0.95) | −2.87 (−2.93, −2.81) |
| | Complications_drugs_antibiotics_pre | −0.03 (−0.07, 0.01) | −1.04 (−1.07, −1.01) |
| | Complications_drugs_hypertension_post | 0.22 (0.06, 0.39) | −4.50 (−4.63, −4.38) |
| | Complications_drugs_heparin_post | 0.16 (0.12, 0.20) | −1.12 (−1.15, −1.09) |
| | Complications_drugs_antibiotics_post | 0.02 (−0.02, 0.06) | −0.67 (−0.70, −0.65) |
| Practices | Practices_progestogen_pre | 0.50 (0.45, 0.56) | −2.19 (−2.24, −2.15) |
| | Practices_cardioaspirin_pre | 0.29 (0.18, 0.41) | −3.76 (−3.85, −3.67) |

for cost variables of type "Complications" and "Practices". The results can be read together with (1) Fig. 5, which reports the average values of the costs; (2) Fig. 6, which reports the percentage of women having that cost greater than zero. In both figures, shadowed bars indicate values where the *p*-value to test the differences among the groups ART vs. No ART (Wilcoxon-test for Fig. 5; Chi square-test for Fig. 6) resulted lower than 0.05 (detailed values are reported in the Section "Descriptives of costs post matching" of the Appendix).

By looking at Fig. 5, the difference of greater magnitude appeared to be related to the hospital admission costs of type "General" referring to the time interval before the delivery (General_hospital_pre), where the average cost was 2235.8€ for ART vs. 624.3€ for No ART. In Table 3, the ART coefficient of the linear regression that examined this variable was 1611.41 (95% CI: 1558.25, 1666.04), which corresponded to the additional cost for ART pregnancies. The information on the intercept of the same regression, which was 624.34 (95% CI: 610.08, 639.05), enabled to have a general picture of the baseline cost accounted for all the pregnant women, and thus to conclude that the ART pregnancies involved a total cost that was more than 3.5 times higher compared to No ART pregnancies. A similar result can be noticed also for the pharmaceutical costs of type "General" referring to the time interval before the delivery (General_hospital_pre): the cost for ART pregnancies (average cost: 375.1€) was around 2.4 times the cost for No ART pregnancies (average cost 159.2€). Significant differences of lower magnitude that went in the same direction (i.e., higher for ART compared to No ART) could be seen also for ED admissions of type "General" and pharmaceutical prescriptions of type "Pregnancy" before the delivery, hospital admissions of both types "General" and "Pregnancy" and also specialistic visits of type "Pregnancy" after the delivery. However, there were also significant differences that went in the opposite direction, thus revealing lower costs for ART compared to No ART pregnancies: specialistic visits of type "General" and "Pregnancy" before the delivery, and pharmaceutical cost and specialistic visits of type "General" after the delivery.

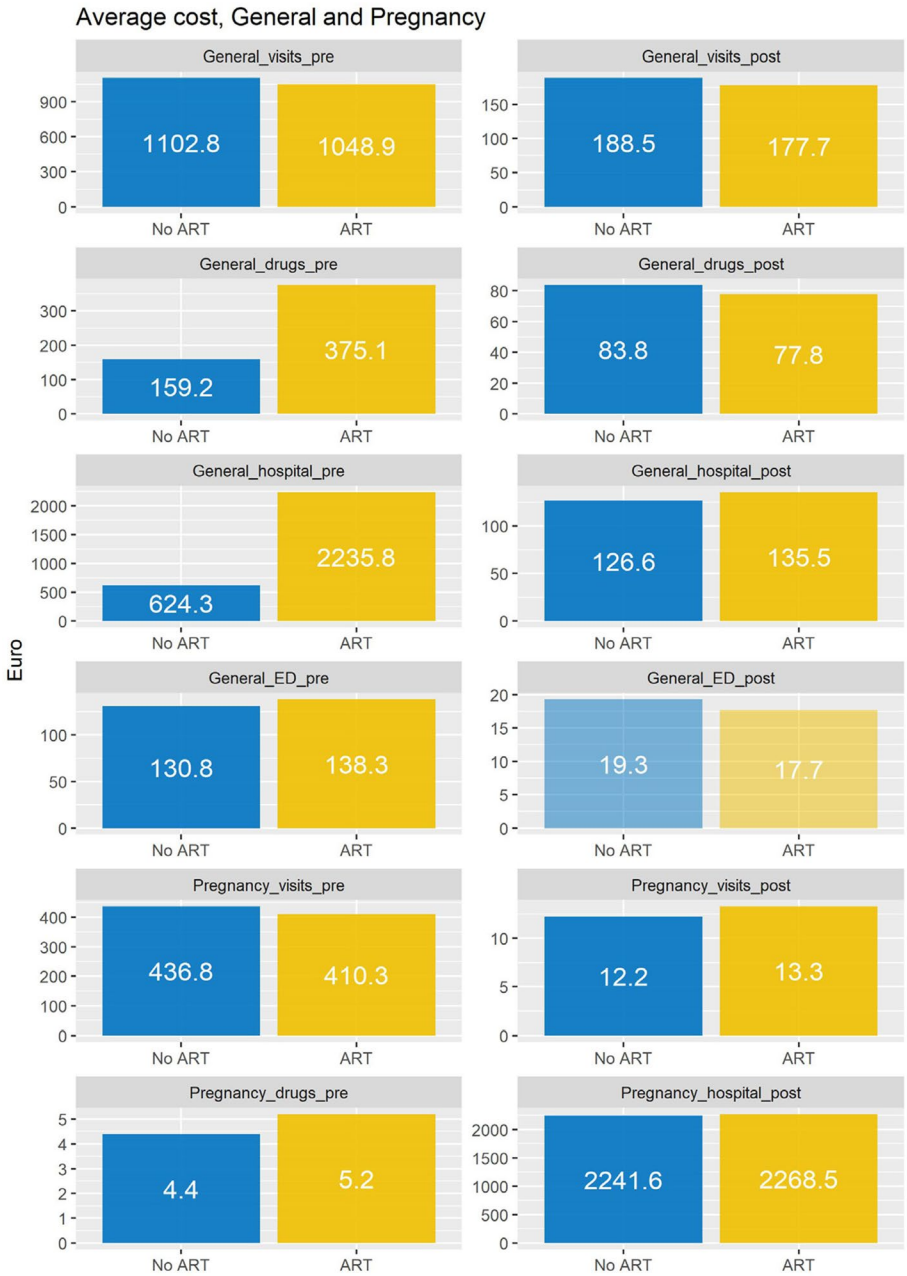


**Fig. 5** Average values of the costs of type General and Pregnancy. Shadowed bars indicate values where the *p*-value of the Wilcoxon-test among the groups ART vs. No ART resulted higher than 0.05

From Fig. 6, higher risks of spending for complications emerged as statistically significant for ART by focusing on prescription of heparin (before and after delivery), drugs for hypertension (after delivery), hospital admissions (before delivery), and specialistic visits (after delivery); lower risk for drugs for diabetes (before delivery). Results for costs of type "Practices" were both significant and quantitatively relevant: the odds of reporting a cost for cardioaspirin was 1.34 (95% CI: 1.20, 1.51) and for progestogen was 1.65 (95%CI: 1.57, 1.75) higher for ART vs. No ART.

Results of regressions where also the interaction term between ART and time was included are not shown, but are available upon request, given they confirmed what already said. Ultimately, these results allow to draw a picture on some temporal variations that affect all the costs,

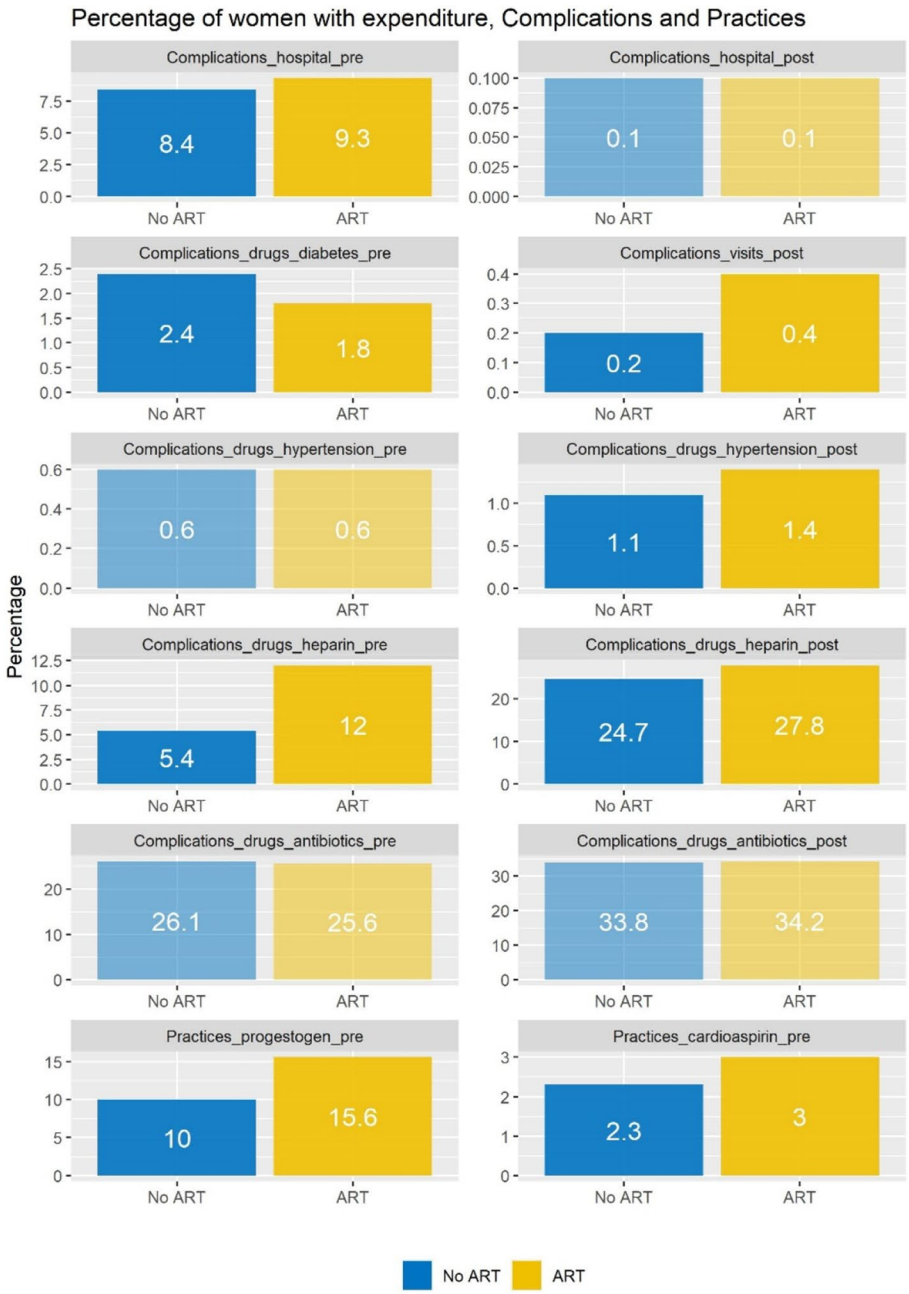


**Fig. 6** Percentage of women having costs of type Complications and Practices greater than zero. Shadowed bars indicate values where the *p*-value of the Chi-square test among the groups ART vs. No ART resulted higher than 0.05

not depending on ART/No ART, as is the case for general drug prescriptions before delivery, which have been decreasing for all pregnancies during the last decade. For some types of costs, looking at the evolution over time reinforces the difference among ART vs. No ART, such as the use of hospital admissions before delivery, which has decreased for No ART while increased for ART. Other coefficients allow to identify trends that seem to be fading, such as the lower cost for specialistic visits before delivery for ART pregnancies.

## Discussion

Within the multiple aspects concerning ART that have raised interest during the last years, economic evaluations are needed to guide strategic decisions on the resources to invest in this innovative service. Thanks to

the magnitude and variety of data available, our study investigates the existence of differences in healthcare costs between ART and spontaneous pregnancies, considering selected confounders, such as personal characteristics of mothers (e.g., age, socio-demographic features, healthcare cost during the year before conception, presence of comorbidity) and information on single/multiple pregnancy. Descriptive results before the matching of the two cohorts, i.e., ART and spontaneous pregnancies, highlight the value-added of our approach, which allow us to draw conclusions that do not depend on (i.e., are controlled for) differences observed in these confounders (such as, for instance, the older age, on average, of women experiencing ART pregnancies).

Our study reports significant higher costs for ART pregnancies, especially in terms of hospital admissions and drug prescriptions occurring before delivery. The differences that can be observed at a general level, i.e., by looking at all the healthcare services, are confirmed by looking into the details of the services related to the pregnancy. However, there are some sources of cost where the direction of results is the opposite, such as that ART pregnancies correspond to lower specialistic visits before and after delivery.

The analysis of costs allows also to take a step further in the identification of the main determinants of the ART economic burden. More specifically, our results support the existence of clinical determinants, given the higher probability of costs for complications incurred by ART pregnancies. Interestingly, our results also reveal the possible existence of social determinants of the ART burden: the two clinical practices investigated (cardioaspirin and progestogen drugs prescriptions) both reveal higher occurrence in ART pregnancies.

We propose an interpretation of our results along three main directions.

A first set of considerations refers to the clinical determinants of the ART burden, focusing on the costs due to increased risk of complications in ART compared to spontaneous pregnancies. Our results add to the clinical evidence produced so far [3, 38] the opportunity to quantify the costs borne by the NHS for the increased complications risk and to identify the specific cost items associated to the type of service provided. As for this aspect, the use of propensity matching techniques enables the consideration of women with same previous characteristics, thus cancelling the noise of previous complications than may have conducted to low fertility and thus ART use. Once having matched the pairs of women, our study enlightens the mechanisms that occur after ART conception, and for this reason the higher costs documented are referred only to specific complications that appear after ART. Since the difference in general costs between ART and no ART women documented in our analysis is greater than the difference found in pregnancy costs, further investigations are needed to identify all the set of clinical conditions (and thus cost items) that fill this gap and contribute to the higher ART general costs.

A second discussion point is related to the social determinants of the ART burden. We believe that the evidence emerging from our results on the clinical practices (i.e., referred to progestogen and aspirin prescriptions) may refer to the need to sustain the evolution of the pregnancy with all available medical tools, particularly supporting the unmet need for psychological and social support for women undergoing ART pregnancies [45]. The anecdotal evidence collected during our study has revealed the possible overuse of some clinical practices during pregnancy care, even if no evidence-based, for emotional and psychological support. This point echoes the literature that has deepened physicians' difficulties in compliance with evidence-based practices at all conditions. A recent work [19] treated this same matter looking at the guidelines recommending waiting the third abortion before offering in-depth examinations to patients. Qualitative methodologies allowed the authors to reveal the internal conflict lived by healthcare professionals, who assist the women experience of psychological emotional discomfort in the waiting situation and are thus willing to anticipate the tests already to previous abortions. An additional consideration comes from principles of social psychology and refer to (i) patients' preferences, which are influenced by multiple factors that may make their choices deviate from evidence-based recommendations and statistical likelihood; (ii) physicians' possibility for mistakes related to cognitive errors when interpreting data, for example being overly influenced by unusual cases that resulted in unexpectedly good outcomes [23]. More in general, healthcare professionals may be influenced in their prescription choices by several factors, related to patients' characteristics [31], or ultimately due to the fear of depriving patients of hope [18].

To reach the advocated balance between research evidence, individual need, and healthcare resources [19], we argue there should exist ad hoc guidelines, developed with all stakeholder's involvement, which clarify how to care for the psychological and social support needed by ART pregnancies, aiming to fill the gap between evidence-based and patient-centred medicine [5]. Such guidelines could identify the healthcare services appropriately devoted to being *pro-gestation*, such as group prenatal care, prenatal education, and peer support programmes, helping couples to develop strong support networks prenatally [27].

Eventually, the complexity of ART calls for organizational considerations, which remain embedded in the mixed combination of private and public services used during pregnancies [53]. Since our data map only the use of public healthcare services, we can only suggest the presence of the use of private services, which however remain hidden in terms of tracking. The results on the lower use of specialistic visits for ART pregnancies may refer also to this. Surely, there is the need of informing women, conceiving both spontaneously and with ART, about the services that are guaranteed by the NHS.

Our study has limitations that are strictly related to the data used, given that our results strongly rely on the capacity of these data to capture what occurs in the reality. In particular, our data prevent from mapping three types of situations: (i) out-of pocket costs, such as drugs that women by on their own or admissions and visits from private providers; (ii) the entire woman's ART journey, starting from the first ART cycle end ending with the successful ART cycle leading up to the live birth; (iii) micro-costing information, which originate the difference between what is reimbursed to hospitals vs. what is really spent. As for the first aspect, it impacts on the use of private services, as mentioned before, and also on some practices such as the use of progestogen drugs, which can be bought also without a medical recipe. As for the second aspect, being unable to monitor all ART attempts of each woman's ART journey, including those that were unsuccessful (i.e., did not lead to a pregnancy or ended with abortions or interrupted pregnancies) also prevent us from having a complete picture of the costs sustained after the choice of undertaking ART. Eventually, as for the third aspect, an example can be given by looking at caesarean deliveries, which in Lombardy are reimbursed as much as natural deliveries, even if differences emerge in micro costing due to the surgical intervention. In this sense, by choosing the NHS perspective we do not consider the economic commitment required to hospitals when treating the caesarean deliveries, which in our matched cohort are 26% in case of No ART pregnancies, 49% in ART pregnancies.

Notwithstanding these limitations, the available data enable a wide snapshot of the magnitude of the costs due to healthcare services in ART and No ART pregnancies, both in terms of time interval observed and number of sources tracked. This richness enables to overcome the general finding of higher costs attributable to ART pregnancies, by disentangling the contribution of higher risks of complications and of diffused clinical practices. Future research may further enrich our effort by enlarging at least three perspectives: (i) the contribution given by the ART techniques used, which differ in terms of multiple aspects, not ultimately their costs; (ii) the wider process starting from the beginning of the ART cycle, which would allow to consider also couple experiencing ART cycles that do not end in a pregnancy but still have important consequences both in terms of their wealth and the healthcare services used; (iii) the pregnancy journey in terms of social and psychological support received, both in case of ART and spontaneous pregnancies, together with the evolution of the psychological wellbeing of women and couples.

## Conclusions

Our study investigated the costs associated with ART pregnancies with the innovative purpose of digging into their determinants. The research highlighted the role of both clinical factors, such as complications, and social factors, including the unmet need for emotional and psychological support, in contributing to the ART burden. The findings underscore the importance of tailored healthcare policies to optimize resource allocation and enhance pregnancy care for ART patients.

## Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s13561-024-00583-7.

Supplementary Material 1.

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**Authors' contributions**

Conceptualisation, E.L., G.E., A.T, F.P., M.F; Data curation, G.E. and M.F.; Formal analysis, E.L. and M.F.; Investigation, E.L.; Methodology, E.L. and M.F.; Supervision, A.T. and G.P.; Validation, E.L., A.T., F.P., G.E. and M.F.; Visualisation, E.L.; Writing—original draft, E.L.; Writing—review and editing, E.L., A.T., F.P., G.E. and M.F. All authors have read and agreed to the published version of the manuscript.

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**Data availability**

The data that support the findings of this study are available from Lombardy Region, but restrictions apply to the availability of these data, which were used under license for the current study, and so are not publicly available. Data are, however, available from the Lombardy Region upon reasonable request.

## Declarations

**Ethics approval and consent to participate**

Since the study is retrospective, an authorisation protocol number by the local ethics committee was not required. All data were completely and permanently anonymised. All procedures were in accordance with the ethical standards of the institutional and national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

**Competing interests**
The authors declare no competing interests.

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## Publisher's Note