ORIGINAL ARTICLE

PREGNANCY AND BIRTH OUTCOMES IN FEMALE WITH AND WITHOUT ASSISTED REPRODUCTIVE TECHNOLOGY IN UKRAINE

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ABSTRACT

The aim: To assess and compare the risk of maternal/perinatal complications and adverse outcomes in pregnancy and childbirth conceived by ART with those conceived naturally in Ukraine.

Materials and Methods: We conducted a retrospective multicenter cohort study from January 1st, 2019 to December 31st, 2021. This study included pregnant women who delivered at 14 Women's Hospitals from 8 regions of Ukraine.

Results: A total of 21,162 pregnancies were included. Of these, there were 19,801 natural pregnancies and 1,361 pregnancies after ART. The proportion of ART pregnancies has increased every year in during study period, peaking in 2021 (6.7%). Data analysis showed that the risks of gestational diabetes, preeclampsia, moderate or severe anemia, liver-related diseases, thyroid-related diseases, preterm birth, placenta previa, postpartum hemorrhage, and cesarean section were significantly increased in ART pregnancy. For neonatal outcomes, women conceived by ART were more likely to have twins. The effects of ART on the risk of premature rupture of membrane, cord entanglement, intrapartum fever, and cesarean section were more pronounced in singletons pregnancies.

Conclusions: Women conceived by ART were at increased risks of several adverse pregnancy outcomes compared with women conceived naturally. Therefore, prenatal and intrapartum monitoring should be strengthened, and neonatal outcomes should be closely observed for ART pregnancy.

KEY WORDS: assisted reproductive technology (ART); pregnancy outcomes; pregnancy complications; perinatal complications; neonatal complications; Ukraine

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INTRODUCTION

Infertility is a global socio-economic, demographic, reproductive health and clinical issue affecting millions of people of reproductive age worldwide. Literature suggests that infertility affects approximately 15% of couples worldwide, accounting for 48.5 million couples [1], and 186 million individuals [2]. The estimated prevalence of infertility in Ukraine were 25,4% [3]. This applies to both primary and secondary infertility of married women. In the last three decades, the population of Ukraine has been rapidly shrinking due to low birth rates. Within 30 years, its population declined by 10.4 million, from a high of 51.9 million in 1991 to 41.5 million in 2020. One of the reasons for the low birth rate is the infertility among married population. According to national statistical reports, the prevalence of current infertility has increased in 3.0 times for the last five years (2016-2020) in Ukraine [3].

One of the effective methods of infertility treatment is assisted reproductive technologies (ART). Since the birth of the first test-tube baby in 1978, ART has become an effective treatment for infertility. With the progress of technology and provision of services, an increasing number of infants are born following ART therapy. In developed countries, ART pregnancies account for 1.5–5.9% of all births [4-7].

With the progress of assisted reproductive technology (ART) and the increasing number of ART pregnancy, its safety has become the focus of attention [8]. ART is used worldwide, at increasing rates, and data show that some adverse outcomes occur more frequently than following spontaneous conception [9]. Some researchers believe that the increased risks of adverse outcomes after ART conception are mainly related to ART manipulation factors [10], which is due to the addition of many non-physiological operations by ART. Other studies have pointed out that different methods of ART may lead to different types of adverse pregnancy outcomes [11]. However, other studies have concluded ART pregnancies do not have increased risks of adverse perinatal outcomes [12, 13]. At present, opinions are too far apart to reach a consensus.

However, current studies and evidence cannot fully elucidate the mechanism by which ART increases the risk of adverse pregnancy outcomes, and the specific mechanism needs further research. Similar studies have not been conducted in Ukraine. Although pregnancies conceived by ART have a higher risk of maternal/perinatal complications, the overall risk of adverse outcomes necessitating advanced obstetric care has not been closely examined. The challenge of a contemporary evaluation of birth outcomes after assisted conception in Ukraine is the lack of national databases.

THE AIM

To assess and compare the risk of maternal/perinatal complications and adverse outcomes in pregnancy and childbirth conceived by ART with those conceived naturally in Ukraine.

MATERIALS AND METHODS

STUDY DESIGN, SETTING, AND POPULATION

This retrospective multicenter cohort study included pregnant women who delivered at 14 Ukrainian Women's Hospitals in 2019–2021. After excluding women who had early abortions (≤12 weeks), or women who were discharged from care during pregnancy, a total of 21,160 pregnancies were included in the data analysis. Two cohorts were created: women who conceived by either intracytoplasmic sperm injection (ICSI), in vitro fertilization (IVF), ovulation induction (OI), gamete intra-fallopian transfer (GIFT), or artificial insemination (AI), were defined as group of ART pregnancy, and women who conceived naturally without ART, were considered as group of naturally pregnancy.

DATA COLLECTION

Data were collected from standardized clinical forms and hospital records after maternity discharge to form the research database. Maternal characteristics of all pregnancies were firstly extracted, including maternal age (year), intrapartum weight (kg), parity, birthplace, menstrual cycle (21–35 days, 36 days- or irregularity), abnormal pregnancy history and history of uterine fibroids. Maternal age was divided into five groups: <25, 25–29, 30–34, 35–39, ≥40 years. Intrapartum body mass index (BMI, kg/m2) was calculated as maternal intrapartum weight divided by the square of height, and classified into four groups: <25, 25–29.9, 30–34.9, ≥35 kg/m2. Parity did not include this pregnancy and was divided into 0 (nulliparae) and ≥1 (multiparae). Abnormal pregnancy history refers to a history of early abortion (≥2 times), intermediate and late abortion, abnormal development, or ectopic pregnancy. In this study we also used the standardized clinical forms and hospital records to obtain data on pregnancy complications, perinatal complications and neonatal outcomes. Data on pregnancy complications included gestational diabetes (fasting glucose concentrations ≥ 5.5 mmol/l or 2-h plasma glucose concentrations ≥ 8.0 mmol/l), preeclampsia (hypertension from 20 weeks' gestation and proteinuria; severe preeclampsia was defined as preeclampsia with either a diastolic blood pressure ≥ 110 mmHg or proteinuria ≥ 5 g/day or both), anemia (hemoglobin < 100 g/l and hematocrit < 0.30; moderate or severe anemia was defined as hemoglobin < 90 g/l or 60 g/l), liver-related diseases (cholestasis, hepatitis, liver function damage, etc.) and thyroid-related diseases (hyperthyroidism, hypothyroidism, thyroiditis, etc.). Data on perinatal complications included hospitalization time (day), preterm birth (<37 weeks' gestation), premature rupture of membrane, amniotic fluid pollution (clear as 0°, I°, II°, or III°), polyhydramnios (>2,000 ml in the third trimester), oligohydramnios (<300 ml in the third trimester), cord entanglement, torsion of cord, intrapartum fever (intrapartum temperature > 38°C), placenta previa, antepartum hemorrhage, postpartum hemorrhage (measured blood loss ≥ 500 ml) and delivery mode (spontaneous labor or cesarean section). And data on neonatal outcomes included gestational weeks in birth, offspring gender, birth weight (g), macrosomia (birth weight ≥ 4,000 g), twins or multiples, fetal distress, stillbirth or abnormal development (fetal malformation).

ETHICS

Ethical clearance for this study was obtained from the ethics committee of the Shupyk National Healthcare University of Ukraine. This study was performed in line with the principles of the Declaration of Helsinki. Written informed consent for participation was not required for this study in accordance with the national legislation and the institutional requirements.

Table I. Patient characteristics between naturally pregnancy (n=19,801) and assisted reproductive technology (ART) pregnancy (n=1,361) in Ukraine (2019-2021).

Variables	All pregnancy n=21,162	Naturally pregnancy	ART pregnancy	p-value
	n (%)	n (%)	n (%)	
Maternal age (year)	29.6±3.9	29.5±3.9	31.6±3.9	0.054
<25	1,327(6.3)	1,316(6.6)	11(0,8)	0.056
26-29	10,462(49.4)	10,105(51.0)	357(26.3)	
30-34	6,904(32.6)	6,358(32.1)	546(40.1)	
35-39	2,112(10.0)	1,813(9.2)	299(22.0)	
≥40	355(1.7)	208(1.1)	147(10.8)	
Intrapartum weight (kg)	70.6±9.1	70.5±9.0	72.8±9.9	0.025
Intrapartum BMI (kg/m^2)	26.8±3.1	26.7±3.2	22.9±3.4	0.03
Parity				0.034
Nulliparae	16,133(76.2)	14,929(75.4)	1,204(88.5)	
Multiparae	5,027(23.8)	4,871(24.6)	156(11.5)	
Birthplace				0.003
Kyiv region	8,412(38.8)	7,730(39.0)	682(50.1)	
Odesa region	3,684(17.4)	3,367(17.1)	317(23.3)	
Lviv region	2,437(11.5)	2,259(11.4)	178(13.1)	
Other regions	6,627(31.3)	6,444(32.5)	183(13.5)	
Menstrual cycle (day)				0.024
21-35	18,101(91.6)	16,995(92.1)	1,106(84.8)	
36 - or Irregularity	1,649(8.4)	1,452(7.9)	197(15.2)	
Abnormal pregnancy history	2,255(11.2)	1,868(9.9)	387(29.1)	0.052
Early abortion (≥2 times)	1,718(8.5)	1,449(7.7)	268(20.2)	0.036
Intermediate and late abortion or abnormal development	420(2.1)	346(1.8)	74(5.6)	0.021
Ectopic pregnancy	323(1.6)	211(1.1)	112(8.4)	0.034
With uterine fibroids	1,129(5.3)	1,016(5.1)	113(8.3)	0.012

Note: ART, assisted reproductive technology; BMI, body mass index

STATISTICAL ANALYSIS

All clinical data were entered in an Excel (Microsoft Corp., Redmond, WA, USA) database for statistical analysis. Results are expressed as median (range), mean ± standard deviation for continuous variables, and number and corresponding percentage for qualitative variables. We compared maternal characteristics and pregnancy outcomes between group of ART pregnancy and group of naturally pregnancy. Continuous variables were described as mean and standard deviation, and categorical variables were displayed as frequency (percentage). All comparisons between groups were conducted using standardized differences, which are not influenced by sample size and have been frequently used in previous large cohort studies. The association between ART using and pregnancy outcomes were evaluated by logistic regression analysis. The crude and adjusted odds ratio (OR) with 95% confidence intervals (95%CI) for pregnancy outcomes were calculated. Adjusted values were adjusted for maternal age, intrapartum BMI, parity, birth plurality and abnormal pregnancy history. All statistical analyses were two-sided and significance was set at $P < 0.05$.

RESULTS

A total of 21,162 women were included in this retrospective cohort study, of whom 1,361 women conceived by ART as group of ART pregnancy, and 19,801 women conceived naturally without ART as group of naturally pregnancy. During study period (2019-2021), the proportion of ART pregnancy has increased each year, reaching a peak in 2021 (6.7%). Of the ART pregnancy, the proportion of pregnant

Table II. The incidence of pregnancy complications between naturally pregnancy (n=19,801) and ART pregnancy (n=1,361) in Ukraine (2019-2021).

Pregnancy complications	All pregnancy (n=21,162)		Naturally pregnancy		ART pregnancy		*p*-value
	n	%	n	%	n	%	
Gestational diabetes	3,884	18.4	3,473	17.5	411	30.2	0.0239
Preeclampsia	805	3.8	673	3.4	132	9.7	0.0169
Severe preeclampsia	267	1.3	216	1.1	51	3.7	0.0114
Anemia	4,683	22.1	4,317	21.8	366	26.9	0.0092
Moderate or severe anemia	747	3.5	677	3.5	70	5.1	0.0079
Liver-related diseases [a]	807	3.8	734	3.7	73	5.4	0.0068
Thyroid-related diseases [b]	1,890	8.9	1,702	8.6	188	13.8	0.0154

[a] included intrahepatic cholestasis, hepatitis, liver dysfunction, liver damage etc.
[b] included hyperthyroidism, hypothyroidism, thyroiditis, thyroid tumor, etc.
ART, assisted reproductive technology

Table III. The incidence of perinatal complications between naturally pregnancy (n=19,801) and ART pregnancy (n=1,361) in Ukraine (2019-2021).

Perinatal complications	All pregnancy (n=21,162)		Naturally pregnancy		ART pregnancy		*p*-value
	n	%	n	%	n	%	
Hospitalization time (day)	4.9±2.3		4.9±2.3		6.8±2.7		0.026
Preterm birth	1,616	7.6	1,327	6.7	289	20.4	0.041
Premature rupture of membrane	5,879	27.7	5,581	28.1	298	21.7	0.013
Amniotic fluid pollution							0.015
Clear (0°)	17,357	82.0	16,154	81.6	1,203	88.4	
I°	1,125	5.3	1,064	5.4	61	4.5	
II°	1,173	5.5	1,127	5.7	46	3.4	
III°	1,488	7.0	1,437	7.3	51	3.7	
Polyhydramnios	571	2.7	524	2.6	47	3.5	0.004
Oligohydramnios	1,374	6.5	1,276	6.4	98	7.2	0.002
Cord entanglement	7,610	36.0	7,143	36.1	467	34.3	0.004
Torsion of cord	662	3.1	617	3.1	45	3.3	0.001
Intrapartum fever	2,376	11.2	2,248	11.4	128	9.4	0.006
Placenta previa	1,138	5.4	1,021	5.2	117	8.6	0.012
Antepartum hemorrhage	74	0.3	68	0.3	6	0.4	0.001
Postpartum hemorrhage	2,272	10.7	2,009	10.1	263	19.3	0.024
Cesarean section	9,041	42.7	8,017	40.5	1,024	75.2	0.075

Note: ART, assisted reproductive technology

women over 35 years old and multiparae increased mildly. In addition, the proportion of women with abnormal pregnancy history in ART pregnancy decreased sharply, and then increased rapidly. Patient characteristics between ART and naturally pregnancy is summarized in Table I.

In this study the mean maternal age and intrapartum BMI of women conceived by ART were significantly higher than those of women conceived naturally. Women conceived by ART were more likely to be nulliparae, more likely to have a long or irregular menstrual cycle and an abnormal pregnancy history (including early abortion, intermediate and late abortion, abnormal development, or ectopic pregnancy), and more likely to have uterine fibroids.

The incidence of pregnancy and perinatal complications in ART and natural pregnancy in Ukraine is presented in Table II, III. In this study statistically significant increases were noted in gestational diabetes (30.2%), preeclampsia (9.7%), thyroid-related diseases (13.8%), preterm birth (20.4%), placenta previa (8.6%), postpartum hemorrhage (19.3%) and cesarean section (75.2%) in ART pregnancy, compared to

Table IV. Neonatal outcomes between naturally pregnancy (n=19,801) and ART pregnancy (n=1,361) in Ukraine (2019-2021).

Neonatal complications	All pregnancy (n=21,162)		Naturally pregnancy		ART pregnancy		*p*-value
	n	%	n	%	n	%	
Gestational weeks	38.8±1.9		38.7±1.8		37.8±2.3		0.051
Birth weight (g)	3,317±506.8		3,331.5±494.5		3,138.5±631.7		0.034
Macrosomia	1,517	7.2	1,437	7.3	80	5.9	0.005
Twins or multiples	526	2.5	244	1.2	282	20.8	0.065
Fetal distress	1,442	6.8	1,367	6.9	75	5.5	0.005
Stillbirth or abdominal development	233	1.1	188	0.9	45	3.4	0.016

Note: ART, assisted reproductive technology

naturally pregnancy. The occurring rates of anemia (26.9%), liver-related diseases (5.4%), polyhydramnios (3.5%), oligohydramnios (7.2%) and torsion of cord (3.3%) were also elevated in ART pregnancy, but with no significant difference (Table III). However, there was a decline in the incidences of premature rupture of membrane (21.7%) and amniotic fluid pollution (I°: 4.5%, II°: 3.4%, III°: 3.7%) in ART pregnancy.

Results of the data analysis of neonatal outcomes between natural pregnancy and pregnancy after ART in Ukraine is presented in Table IV. Data analysis showed that the average birth weight in ART pregnancy was significantly lower than in natural pregnancy. In this study significant rises of incidence were observed in twins or multiples (20.8%) and stillbirth or abnormal development (3.4%) in ART pregnancy. No significant difference was noted in macrosomia and fetal distress between the two groups.

Multivariable logistic regression analysis showed that the association between ART and pregnancy outcomes were significant. All the pregnancy complication listed, including gestational diabetes, preeclampsia, moderate or severe anemia, liver-related diseases, and thyroid-related diseases, were more likely to occur among women conceived by ART.

In this study (risk for perinatal complications), the risk of preterm birth, placenta previa, postpartum hemorrhage, and cesarean section were significantly increased, while the risk of premature rupture of membrane, amniotic fluid pollution, cord entanglement, and intrapartum fever were significantly decreased in ART pregnancy as compared with naturally pregnancy. For neonatal outcomes, women conceived by ART were more likely to have twins or multiples, and the risk of stillbirth or abnormal development was also significantly increased. Moreover, the risk of macrosomia and fetal distress were significantly decreased in ART pregnancy.

This study showed that when restriction to singletons, the risks of adverse pregnancy outcomes were reduced. The effects of ART on the risk of premature rupture of membrane, cord entanglement, intrapartum fever, cesarean section, and stillbirth or abnormal development were more pronounced among singleton pregnancies compared with that among pregnancies of twins or multiples, while the effect of ART on the risk of polyhydramnios was more prominent among pregnancies of twins or multiples.

DISCUSSION

To our knowledge, this is the first epidemiological study that focuses on pregnancy and birth outcomes in female with and without assisted reproductive technology in Ukraine. The present retrospective cohort study was conducted to compare maternal and neonatal outcomes between ART and naturally pregnancies, and in addition to explore the association of ART with adverse pregnancy outcomes by stratifying on birth plurality and maternal age in Ukraine. A total of 21,162 pregnancies were included. Of these, there were 19,801 natural pregnancies and 1,361 pregnancies after ART. The proportion of ART pregnancies has increased every year in during study period, peaking in 2021 (6.7%). Data analysis showed that the risks of gestational diabetes, preeclampsia, moderate or severe anemia, liver-related diseases, thyroid-related diseases, preterm birth, placenta previa, postpartum hemorrhage, and cesarean section were significantly increased in ART pregnancy. For neonatal outcomes, women conceived by ART were more likely to have twins. The effects of ART on the risk of premature rupture of membrane, cord entanglement, intrapartum fever, and cesarean section were more pronounced in singletons pregnancies. We found a increase in the incidence of multiple births in ART pregnancies compared to naturally pregnancies. In the present study, the increased risks were found in ART pregnancy compared with naturally pregnancy: gestational diabetes, preeclampsia, moderate or severe anemia, liver-related diseases, thyroid-related diseases, preterm birth, placenta previa, postpartum hemorrhage, cesarean section, and stillbirth or abnormal development, which were largely consistent with the findings of previous studies [8, 14, 15].

The International Committee for Monitoring Assisted Reproductive Technologies (ICMART) annual world report series provides an important instrument for tracking trends in ART treatment and for providing clinical and public health data to ART professionals, health authorities, patients and the general public. ART is increasingly influencing the fertility trends of high-income countries characterized by a pattern of delayed childbearing. However, research on the impact of ART on completed fertility is limited and the extent to which delayed births are realized later in life through ART is not well understood. ART includes all infertility treatments to achieve conception; IVF is the process by which an oocyte is fertilized by semen outside the body; non-IVF ART treatments include ovulation induction, artificial insemination, and intrauterine insemination. IVF represents only a small portion of all infertility treatment used in Ukraine. It is well established that both IVF and subfertility, independent of treatment, are associated with compromised maternal and infant perinatal outcomes. As these and other reproductive technologies expand, leading to a substantial number of successful pregnancies and births, it is critical for prospective parents to understand the maternal and neonatal outcomes associated with ART. Several studies have shown that ART pregnancies have an increased risk of multiple pregnancy and adverse pregnancy outcomes, including gestational diabetes, gestational hypertension, placenta previa, preterm birth, operative delivery, low birth weight, birth defects and perinatal mortality [8, 16-18]. However, other studies have concluded ART pregnancies do not have increased risks of adverse perinatal outcomes [4, 7, 12, 13, 19]. The incidences of small for gestational age, preterm birth and cesarean section are similar between ART and naturally pregnancies. It is not clear whether the increased risk of adverse pregnancy outcomes is due to ART itself, multiple births, or potential infertility.

Infertility affects one in seven couples, and many of these need ART. To date, more than 8 million children have been conceived after ART globally [20], and up to 6% (range between 0.2% and 6.4%) of the European birth cohorts is conceived by ART [4]. ART is widely practiced throughout the world but continues to be characterized by significant disparities in utilization, practice, effectiveness and safety. ART involves standard in vitro fertilisation (IVF) and intracytoplasmic sperm injection (ICSI). In literature there is increasing evidence that infertility or subfertility is an independent risk factor for obstetrical complications and adverse perinatal outcomes, even without the addition of assisted human reproduction. Multiple pregnancy is the most powerful predictive factor for adverse maternal, obstetrical, and perinatal outcomes. Couples should be thoroughly counselled about the significant risks of multiple pregnancies associated with all assisted human reproductive treatments. Among singleton pregnancies, assisted reproductive technology is associated with increased risks of preterm birth and low birth weight infants, and ovulation induction is associated with an increased risk of low-birth-weight infants. Until sufficient research has clarified the independent roles of infertility and treatment for infertility, couples should be counselled about the risks associated with treatment. Women and couples considering assisted human reproduction and concerned about perinatal outcomes in singleton pregnancies should be advised that (1) intracytoplasmic sperm injection does not appear to confer increased adverse perinatal or maternal risk over standard in vitro fertilization, and (2) the use of donor oocytes increases successful pregnancy rates in selected women, but even when accounting for maternal age, can increase the risks of low birth weight and preeclampsia. Any ART procedure should be prefaced by a discussion of fetal outcomes and the slight increase in the risk of congenital structural abnormalities, with emphasis on known confounding factors such as infertility and body mass index. In pregnancies achieved by artificial reproductive technology, routine anatomic ultrasound for congenital structural abnormalities is recommended between 18 and 22 weeks.

Despite the continuous technological improvements, ART cannot fully compensate for the age-related decline in female reproductive performance because the effectiveness of ART also declines with age [21. 22]. The total number of ART births is directly influenced by ART treatment and success rates and indirectly shaped by further childbearing postponement, which leads to a higher proportion of women seeking to have children at older ages when their reproductive potential diminishes. However, alternative treatment options such as oocyte cryopreservation (egg freezing) or the use of third-party eggs from younger donors are expanding women's reproductive potential. Our prognosis suggest that increases in ART fertility rates will be mainly driven by an increase in the demand for infertility treatment. However, the diffusion of alternative treatment options, such as egg freezing and the use of third-party donor eggs, may lead to a sharp rise in ART success rates and alter these dynamics in the future.

STRENGTHS AND LIMITATION

This study has several strengths. First, this is the first multicenter cohort study was aimed to assess and compare the risk of maternal/perinatal complications and adverse outcomes in pregnancy and childbirth conceived by ART with those conceived naturally in Ukraine. Second, large size of the sample and the fact that it is population-based, which allowed us to conduct further subgroup analysis with enough power. Clinicians will be better informed about the adverse outcomes that have been documented in association with ART, including obstetrical complications, adverse perinatal

outcomes, multiple gestations, structural congenital abnormalities, chromosomal abnormalities, and imprinting disorders. However, there are some limitations in this study. The limitations of this study include its retrospective design and including 33.3% regions (8 from 24) in Ukraine. The results may not be representative of other regions of Ukraine. Therefore, we should be cautious in generalizing our findings to other Ukrainian regions. Second, we did not collect information on the ART form. Third, the retrospective design of this study could not assess a causal relationship between ART and adverse pregnancy outcomes. These limitations should be considered in future studies. However, this study provides valuable data as a first study for possible comparison with data from other countries.

CONCLUSIONS

This study showed the widespread application of ART in Ukraine, with the proportion of ART pregnancies increasing in the study period, and confirmed the increased risks of several adverse pregnancy outcomes in ART pregnancies. We found a increase in the incidence of multiple births in ART pregnancies compared to naturally pregnancies. In the present study, the increased risks were found in ART pregnancy compared with naturally pregnancy: gestational diabetes, preeclampsia, moderate or severe anemia, liver-related diseases, thyroid-related diseases, preterm birth, placenta previa, postpartum hemorrhage, cesarean section, and stillbirth or abnormal development, which were largely consistent with the findings of previous studies. Obstetricians should be aware of the increased risk of adverse outcomes among this population. Therefore, prenatal and intrapartum monitoring should be strengthened, and neonatal outcomes should be closely observed for ART pregnancy. More research should be conducted to further clarify whether the increased risk of adverse pregnancy outcomes is due to ART itself or other factors.

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