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Article

A 10-Year Observational Study on Twin Pregnancy: Role of Fetal Sex Pairing on Obstetric Outcome

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Abstract

Fetal sex contributes to the determination of obstetric outcome, as pregnancies carrying male babies seem to have an increased risk of maternal-fetal complications. Most studies have been conducted on singleton pregnancies, whereas less evidence is available for twins. A 10-year retrospective observational study was conducted on a cohort of 1180 women with twin pregnancy delivered at a single tertiary hospital. Clinical data on maternal characteristics, and obstetric and neonatal outcomes were collected, and the analysis was performed on monochorionic (MC) and dichorionic (DC) diamniotic twins separately. The group of DC twins included 837 cases, and those conceived by assisted reproductive technologies (ART) were more likely to have one or both female fetuses rather than males. The incidence of hypertensive disorders of pregnancy (HDP) was higher in same-sex pairs than in opposite-sex pairs. No differences were found regarding other obstetric and neonatal outcomes among the three sex-pairing groups. The MC twins group included 228 cases, and in female-carrying pregnancies a higher incidence of gestational diabetes (GDM) was observed compared to the male group. Furthermore, male pairs had significantly lower Apgar scores than females. Fetal sex seems to have a mild effect in twins compared to singleton pregnancies, suggesting a more complex set of factors contributing to pregnancy outcome in multiple pregnancies. However, we observed a higher incidence of HDP among same-sex DC pairs, a higher rate of GDM among MC female-female pairs, and a worse adaptation to extrauterine life among male-male pairs in MC twins.

Keywords: Fetal sex; Gender pairing; Gestational diabetes; Hypertensive disorders of pregnancy; Twin pregnancy

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During the past two decades, several evidences have shown the role of fetal sex in pregnancy outcome. In singleton pregnancies a sex-related increased risk of adverse obstetric and neonatal outcome is well established (Al-Qaraghouli & Fang, 2017). Male fetal sex is an independent risk factor for preterm birth (PTB) (Brettell et al., 2008; Challis et al., 2013; Ingemarsson, 2003; Zeitlin et al., 2004), gestational diabetes (GDM), and macrosomia and cord complications (cord prolapse, nuchal cord, true umbilical cord knots) (Sheiner et al., 2004; Verburg et al., 2016). Males also have a higher risk of complications during labor and delivery, such as failure to progress during the first and second stages of labor (Sheiner et al., 2004), nonreassuring fetal heart patterns (Dawes et al., 1999; Porter et al., 2016), cesarean section (CS) delivery (Eogan, 2003; Lurie et al., 2004), and neonatal morbidity and mortality (Mondal et al., 2014; Stevenson, 2000).

Available data support the hypothesis that male sex is an offending factor, whereas female sex a protective one; however, the mechanisms underlying these observations remain unclear. Presumably, the hormonal environment the fetus is exposed to during pregnancy is the main conditioning factor. For instance, the observation that female fetal sex would increase the risk of hypertensive disorders during pregnancy (HDP) is supported by the potential role of elevated levels of maternal serum human chorionic gonadotropin in pregnancies carrying females compared to those carrying males (Zheng et al., 2016) or the elevated levels of angiotensin at 15 weeks only in pregnancies carrying females compared to controls (Sykes et al., 2014). Besides, the placental vascular bed seems to be more responsive to magnesium sulphate in preterm female than male pregnancies, so females would have better fetal nutrient delivery and gas exchange than males (Gray et al., 2015). These observations show how fetal sex represents an interactive factor between the mother, the placenta, and the fetus (Al-Qaraghouli & Fang, 2017).

With this background, twin pregnancies represent a unique opportunity to explore the effect of fetal sex in pregnancy complications, given the same-sex pairs and opposite-sex pairs may present also different hormonal phenotypes. Some previous studies analyzed the impact of fetal sex on pregnancy and perinatal outcome among twins, but results are heterogeneous and debatable, considering also the effect of chorionicity (Derom et al., 2005; Esposito et al., 2023; Funaki et al., 2022; Goldman et al., 2003; Luke et al., 2005; Shinwell et al., 2007; Tan et al., 2004).

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Thus, the aim of the study is to establish the role of fetal sex pairing on obstetric and perinatal outcome in dichorionic (DC) and monochorionic (MC) twin pregnancies managed in a single referral center over a 10-year period.

Materials and Methods

A retrospective observational study was conducted on a cohort of 1180 twin pregnancies delivered from 2010 to 2020 at Careggi University Hospital, a tertiary hospital in Florence, Italy. The sample population was restricted to women with twin pregnancies who delivered later than 22 weeks. Triplets and higher order multiple pregnancies were excluded. In addition, pregnancies with at least one infant with a birth defect (6.1%) were not included.

Obstetric digital records were used to extrapolate data regarding maternal characteristics, such as maternal age, body mass index (BMI), parity, mode of conception (i.e., spontaneous conceived [SC] or assisted reproductive technologies [ART]], and complications that occurred during pregnancy. Furthermore, all data regarding labor and delivery, including neonatal outcome, were collected. Women with any missing data regarding fetal sex, birth weight, gestational age at birth, or unreliable data on chorionicity were excluded.

The analysis was performed on monochorionic (MC) and dichorionic (DC) twin pregnancies separately. Twin pregnancies were classified into three groups based on fetal sex pairing (female-female, male-male and female-male pairs), compared in terms of maternal characteristics, pregnancy and perinatal outcomes. The binary sex categorization (male or female) was designated at birth, based on the visible external anatomy of the newborn.

The study aimed to evaluate the following obstetric outcomes, defined according the most recent international guidelines: hypertensive disorders of pregnancy (HDP), gestational diabetes (GDM), fetal growth restriction (FGR), obstetric cholestasis, spontaneous preterm birth (sPTB), premature preterm rupture of membranes (pPROM) and intrauterine fetal demise (IUFD). Pregnancy dating and gestational age at delivery were based on last menstrual period in spontaneous conceived twins, confirmed during the first ultrasound examination. ART twins' dating was based on the egg retrieval in fresh cycle conceived pregnancies or on the age of the frozen embryo at the time of transfer in frozen cycle conceived pregnancies.

Data on labor and delivery outcome included the onset of labor (spontaneous or induced), mode of delivery, gestational age at delivery, and postpartum blood loss. Neonatal data comprised birth weight, Apgar score at 5 and 10 minutes, arterial pH, need for neonatal resuscitation, and neonatal intensive care unit (NICU) admission.

Data analysis was performed by IBM SPSS version 22 (IBM, Armonk, NY, USA) statistical software package. Data distribution was evaluated by the D'Agostino and Pearson omnibus normality test. All outcomes of DC twins were investigated, comparing the female-female, male-male, and female-male groups by using chi-square test and analysis of variance (ANOVA) test, as appropriate. Data from MC twin male pairs versus female pairs were compared by using Fisher's exact test or chi-square test and *t* Student test or Mann-Whitney test, as appropriate. *P*-values of <.05 represent statistical significance.

Results

Maternal characteristics among DC twin pregnancies ($n = 837$) and MC twin pregnancies ($n = 228$) are reported in Table 1 and Table 2 respectively. Among DC twins, 27.9% carried female-female twin pairs, 30.3% male-male twin pairs and 41.8% discordant sex pairs. In the MC twin group 49.1% was represented by female-female twin pairs. More than half of pregnant women included among DC twin pregnancies and 35% among MC twin pregnancies were over 35 years and most were nulliparous. Maternal age, pregestational BMI and parity were similar and there was no statistical difference in terms of gestational age at delivery between fetal sex groups among both DC and MC twin pregnancies.

In DC twin pregnancies, those conceived from ART were more likely to have one or both female fetuses ($p = .008$) and the majority (60.1%) carried opposite-sex pairs. Most were conceived after in vitro fertilization (FIVET; 48.3%), and just a minority after intracytoplasmic sperm injection (ICSI; 7.6%). On the contrary, the mode of conception and the rate of ART-conceived pregnancies among female MC twin pairs were similar to male MC twin pregnancies.

Pregnancy and perinatal outcome of DC and MC twin pregnancies are reported in Table 3 and Table 4 respectively. In the DC pregnancies group, GDM was the most frequent observed complication (19.9%). The incidence of adverse pregnancy outcome such as GDM and cholestasis was similar between the three groups: fetal sex pairing was not independently associated with either of these outcomes.

Hypertensive disorders complicated 7.2% of all DC pregnancies recruited, and the incidence was higher in male-male pairs (11%) than in other groups ($p = .01$). Particularly gestational hypertension contributes to this result (10.7% of male-male pregnancies), whereas the incidence of preeclampsia was very low (overall 1.1% of all DC pregnancies and 0.4% of male-male pregnancies). Only one case of HELLP syndrome was recorded (in the female-female group). sPTB (before 37 weeks) was observed in 18% of cases and only 4% before 28 weeks; the incidence of pPROM in the study population was 10.5%, with no significant difference in the rate of prematurity between groups. FGR of at least one fetus complicates 15.6% of pregnancies, and the frequency of IUFD was low (0.9%). The incidence of adverse fetal outcomes was similar in the three groups. Half of all cases (50.9%) were delivered by elective cesarean section (CS), with similar percentages for both CS (both elective and emergency) and vaginal birth among the three groups (Table 3).

Among MC twin pregnancies, FGR was the most frequent pregnancy complication (18.8%), and the incidence was similar among female-to-male twin pairs. Only a few cases reported IUFD, but no difference between the two groups was observed, even though a trend was observed in increased rate of FGR, IUFD and sPTB in males than females, and male pairs were more likely to report an Apgar score <7 at 5 minutes. GDM complicated 13.5% of all MC pregnancies, and the comparison between female-female and male-male pairs showed a significantly higher incidence in pregnancies carrying females ($p = 0.028$). The incidence of other pregnancy complications, such as HDP and obstetric cholestasis, was similar between the two groups. pPROM and sPTB occurred similarly in both female- and male-carrying MC pregnancies. However, a trend was observed in increased rate of FGR, IUFD and sPTB less than 28 and 32 weeks in males than females. Most of the MC twin pregnancies (61.4%) were delivered by elective CS, with no difference between female and male twin pairs. In terms of fetal outcome, sex pairing does not affect the incidence of low arterial pH at birth, whereas it seems to affect the need for neonatal resuscitation. Despite the limited number of cases, both in DC and MC twin pregnancies the first twin of female-female pairs have a

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Table 1. Maternal characteristics according to sex pairing among DC twins ($N = 837$).

	Female-female fetuses ($n = 232$)	Male-male fetuses ($n = 255$)	Female-male fetuses ($n = 350$)	p
Maternal age	35.6 ± 5.2	34.8 ± 5.6	35.7 ± 5.5	.115
Age > 35	135 (58.2%)	130 (51.0%)	202 (57.7%)	.177
Age > 40	43 (18.5%)	50 (19.6%)	86 (24.6%)	.156
Non-Caucasian ethnicity	57 (24.9%)	67 (27.0%)	68 (19.5%)	.078
BMI	22.9 ± 4.1	22.6 ± 4.1	22.8 ± 4.1	1.000
BMI > 35	6 (2.9%)	6 (2.7%)	5 (1.6%)	.539
Nulliparity	169 (72.8%)	168 (65.9%)	255 (72.9%)	.125
Recurrent pregnancy losses	5 (2.2%)	9 (3.5%)	15 (4.3%)	.387
Previous CS	12 (5.2%)	19 (7.5%)	30 (8.4%)	.479
ART conception	136 (58.6%)	124 (48.6%)	213 (60.9%)	.008
FIVET	66 (29.3%)	37 (27.4%)	98 (43.8%)	
ICSI	22 (15.0%)	35 (25.9%)	17 (7.6%)	
Oocyte donation IVF	18 (7.7%)	24 (9.4%)	25 (7.1%)	.338

Note: CS, cesarean section; ART, assisted reproductive technology. Continuous variables are expressed as mean ± *SD*; categorical variables are expressed as *n* (%). $p < .05$ indicates statistical significance.

Table 2. Maternal characteristics according to sex pairing among MC twins ($N = 228$)

	Female-female fetuses ($n = 112$)	Male-male fetuses ($n = 116$)	p
Maternal age	33.1 ± 5.4	33.2 ± 5.9	.832
Age > 35	38 (33.6%)	44 (37.9%)	.497
Non-Caucasian ethnicity	21 (18.6%)	26 (22.8%)	.432
BMI	22.1 ± 3.7	22.5 ± 4.0	.524
BMI > 35	3 (2.7%)	6 (5.5%)	.288
Nulliparity	66 (59.8%)	67 (56.9%)	.205
Recurrent pregnancy losses	1 (0.9%)	1 (0.9%)	.980
Previous CS	12 (5.2%)	19 (7.5%)	.479
ART conception	12 (10.6%)	14 (12.1%)	.730

Note: MC, monochorionic; CS, cesarean section; ART, assisted reproductive technology. Continuous variables are expressed as mean ± *SD*; categorical variables are expressed as *n* (%). $p < .05$ indicates statistical significance.

worse adaptation to extrauterine life and increased need of neonatal care and resuscitation at birth compared to those from male-male or discordant pairs. Male pairs among MC twin pregnancies were more likely to report an Apgar score <7 at 5 minutes (Table 4).

Discussion

Our study results show a higher incidence of HDP among same-sex DC pairs, while a higher rate of GDM among MC female-female pairs and a worse adaptation to extrauterine life among male-male pairs in MC twins are reported.

Previous studies found female sex as an independent risk factor for hypertensive disorders in singleton pregnancies, and a higher incidence of HDP in twin pregnancies carrying females than in those carrying males was reported (Funaki et al., 2022; Shiozaki et al., 2011). Our results interestingly suggest a more relevant effect of sex pairing rather than sex itself, with a higher rate of HDP, particularly gestational hypertension, in DC same-sex than sex-discordant twins, under the assumption of a worse placentation process for an enhanced hormonal background in same-sex pairs. The high serum androgen levels of women carrying male-male twin pregnancies may have a harmful effect on the vascular endothelium, by activation of inflammatory mechanisms and oxidative stress (Moretti et al., 2017). Similarly, in female-female couples, this result could be explained by the elevated levels of maternal serum hCG and angiotensin (Sykes et al., 2014; Zheng et al., 2016). Furthermore, a recent systematic review and meta-analysis demonstrated that twin pregnancies with a female fetus were more likely to be associated with preterm preeclampsia, whereas those carrying a male were more likely to develop term preeclampsia (Broere-Brown et al., 2020).

In our cohort women carrying female-female MC twin pregnancies showed a significantly higher incidence of GDM compared to those carrying male-male pairs. Probably in female-female pairs, which are known to be more frequent following ART

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Table 3. Pregnancy and perinatal outcome according to sex pairing among DC twins

	Female-female fetuses ($n = 232$)	Male-male fetuses ($n = 255$)	Female-male fetuses ($n = 350$)	p
HDP	23 (9.5%)	27 (10.6%)	20 (5.7%)	**.027**
• Gestational hypertension	19 (8.2%)	26 (10.2%)	14 (4.0%)	
• Preeclampsia	2 (0.8%)	1 (0.4%)	6 (1.7%)	
• HELLP syndrome	1 (0.4%)	0 (0.0%)	0 (0.0%)	
Gestational diabetes	53 (22.8%)	50 (19.6%)	59 (16.9%)	.200
FGR (at least 1 fetus)	27 (11.6%)	38 (14.9%)	57 (16.3%)	.293
Obstetric cholestasis	14 (6.0%)	26 (10.2%)	28 (8.0%)	.243
Intrauterine death	2 (0.9%)	2 (0.7%)	3 (0.8%)	.994
Admission for threatened labor	36 (15.5%)	43 (16.9%)	59 (16.9%)	.896
pPROM	25 (10.8%)	24 (9.4%)	37 (10.6%)	.860
sPTB	46 (19.8%)	41 (16.1%)	66 (18.9%)	.528
sPTB <28 weeks	12 (5.2%)	11 (4.3%)	11 (3.1%)	.464
sPTB <32 weeks	20 (8.7%)	20 (7.8%)	33 (9.4%)	.792
Induction of labor	20 (8.6%)	20 (7.9%)	31 (8.9%)	.834
Mode of delivery • Vaginal delivery • Elective CS • Emergency CS in labor • Emergency CS (not in labor)	 34 (14.7%) 113 (48.7%) 30 (12.9%) 51 (22.0%)	 26 (10.2%) 133 (52.2%) 34 (13.3%) 56 (22.0%)	 38 (10.9%) 182 (52.0%) 50 (14.3%) 66 (18.9%)	.748
Gestational age at delivery	35.03 ± 3.0	34.9 ± 3.1	34.9 ± 3.0	.779
Birth weight (g)	2215 ± 568 2184 ± 570	2328 ± 582 2231 ± 608	2295±572 2244±577	.082 .471
Apgar score at 5 min <7	3 (1.3%)	4 (1.6%)	5 (1.4%)	.968
Arterial cord pH (<7.2)	11 (4.8%)	19 (7.6%)	13 (3.7%)	.110
Neonatal resuscitation	First twin 5 (2.2%) Second twin 4 (1.8%)	First twin 2 (0.8%) Second twin 3 (1.2%)	First twin 0 (0%) Second twin 2 (0.6%)	.020 First twin .136 Second twin
Maternal postpartum blood loss • 500–1000 milliliters • >1000 milliliters	31 (32.3%) 15 (15.6%)	40 (35.1%) 23 (20.2%)	36 (35.3%) 16 (15.7%)	.807

Note: DC, dichorionic; HDP, hypertensive disorders of pregnancy; pPROM, premature preterm rupture of membranes; sPTB, spontaneous preterm birth; CS, cesarean section. Continuous variables are expressed as mean ± *SD*; categorical variables are expressed as *n* (%). $p < .05$ indicates statistical significance.

as mode of conception (Scott Sills et al., 2000), the high incidence of dysmetabolic pathologies and insulin resistance, a contributing factor for infertility, may have played a relevant role. Also, a female fetus is thought to be associated with greater maternal insulin resistance during pregnancy (Xiao et al., 2014), and higher leptin and C-peptide concentrations were observed in female neonates cord blood (Walsh et al., 2015).

In terms of perinatal outcome, our results show that male pairs from MC twin pregnancies were more likely to report an Apgar score <7 at 5 minutes, confirming previous evidence, where male neonates have a higher rate of respiratory and neurologic morbidity compared to females (Melamed et al., 2009). This disadvantage may be partly justified by the androgen conditioning role on fetal lung development (Hanley et al., 1996; Tremblay & Provost, 2006). As additional proof, a better adaptation and a lower incidence of respiratory distress syndrome, intraventricular hemorrhage (IVH) and convulsions were observed in female neonates from female-female pairs compared with females from unlike-sex twin pregnancies. Thus, the presence of a male rather than a female co-twin would be a risk factor for adverse neonatal outcome (Melamed et al., 2009).

It is well known that PTB is a common complication of twin pregnancies, either after spontaneous labor or iatrogenic delivery. In singletons, male sex seems to be a risk factor for PTB (Astolfi & Zonta, 1999; Challis et al., 2013; Vatten & Skjaerven, 2004; Zeitlin et al., 2004), particularly sPTB (Verburg et al., 2016), highlighting a possible association between spontaneous preterm labor and androgen levels (Cathey et al., 2021; Makieva et al., 2014). However, in the current study we found no significant difference in the incidence of late, very and extremely sPTB in terms of sex-pairing groups, in both DC and MC twins. The available literature suggests that sharing the womb with a male co-twin involves a higher risk of PTB (Derom et al., 2005; Glinianaia, 1998; Loos et al., 2001; Tan et al., 2004), and this risk is greater in male-male pairs than in male-female pairs (Funaki et al., 2022; Melamed et al., 2009). Nevertheless, in most cases, previous studies present heterogeneous data without differentiating between spontaneous and iatrogenic PTB, whereas in our

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Table 4. Pregnancy and perinatal outcome according to sex pairing among MC twins

	Female-female fetuses ($n = 112$)	Male-male fetuses ($n = 116$)	p
HDP	3 (2.7%)	6 (6.2%)	.482
• Gestational hypertension	3 (2.7%)	5 (4.3%)	
• Preeclampsia	0	1 (0.9%)	
Gestational diabetes	21(18.6%)	10 (8.6%)	.028
FGR (at least 1 fetus)	23 (20.5%)	20 (17.2%)	.525
Obstetric cholestasis	11 (9.7%)	5 (4.3%)	.107
Intrauterine death	1 (0.9%)	4 (3.4%)	.184
Admission for threatened labor	16 (14.2%)	11 (9.5%)	.273
PPROM	25 (10.8%)	24 (9.4%)	.860
sPTB	14 (13%)	15 (13.2%)	.966
sPTB <28 weeks	3 (2.7%)	4 (3.5%)	.719
sPTB <32 weeks	6 (5.3%)	11 (9.5%)	.228
Induction of labor	1 (0.9%)	1 (0.9%)	.675
Mode of delivery • Vaginal delivery • Elective CS • Emergency CS in labor • Emergency CS (not in labor)	 6 (5.4%) 69 (61.6%) 8 (7.1%) 29 (25.9%)	 7 (6.0%) 71 (61.2%) 13 (11.2%) 25 (21.6%)	.472
Gestational age at delivery	33.8 ± 2.4	33.9 ± 2.4	.779
Birth weight (g)	1988 ± 478 1920 ± 481	2114 ± 57 2060 ± 555	.062 .045
Apgar score at 5 min <7	5 (4.6%)	15 (13.3%)	.025
Arterial cord pH <7.2	4 (3.8%)	3 (2.6%)	.515
Neonatal resuscitation	8 (7.1%)	5 (4.3%)	.287
Maternal postpartum blood loss • 500–1000 milliliters • >1000 milliliters	16 (37.2%) 6 (14%)	15 (41.7%) 4 (11.1 %)	.786

Note: MC, monochorionic; HDP, hypertensive disorders of pregnancy; pPROM, premature preterm rupture of membranes; sPTB, spontaneous preterm birth; CS, cesarean section. Continuous variables are expressed as mean ± *SD*; categorical variables are expressed as *n* (%). $p < .05$ indicates statistical significance.

cohort we accurately identified only cases where delivery occurred after labor started spontaneously.

Another adverse outcome linked to fetal male sex is stillbirth; in singleton pregnancies carrying male fetuses the risk of stillbirth is up to 10% higher than female ones (Wong et al., 2023). In our population study, even though fetal sex pairing does not significantly affect the risk of IUDF, a higher trend may be pointed out among male pairs, confirming the few data currently available on twins (Funaki et al., 2022).

Despite the trend of IUFD among male pairs, no significant difference in fetal growth abnormalities was observed in our cohort based on fetal sex pairing, which seems not to affect the incidence of FGR, confirming some recent evidences (Funaki et al., 2022). Previous data observed that male neonates from male-male pairs have a lower mean birth weight and a higher rate of FGR compared with those from male-female pairs (Melamed et al., 2009), but data are still conflicting, given also the mutual hormonal influence of unlike-sex pairs (De Zegher et al., 1998; Glinianaia, 1998; James, 2002).

A major strength of this study is the inclusion of a large number of twin pregnancies with strict inclusion criteria and reliable information regarding maternal and obstetric outcome. Besides, data were collected from a single referral center, which enabled a consistent evaluation of outcomes, given the uniformity in clinical practice. Among DC twins, the analysis comparing the three fetal sex-pairing groups ensures an accurate evaluation of the mutual influence among unlike-sex pairs of twins. Nevertheless, some limitations need to be acknowledged, as, for instance, the analysis of data from 10 years of observation entails different clinical approaches and management across time. For instance, ultrasound criteria for FGR identification and diagnostic criteria for HDP or GDM changed across this time spam.

In conclusion, fetal sex seems to have a mild effect in twin than in singleton pregnancies, suggesting a more complex set of factors contributing to pregnancy outcome in multiple pregnancies. However, we observed a higher incidence of HDP among same-sex DC pairs, and a higher rate of GDM among MC female-female pairs and a worse adaptation to extrauterine life among male-male pairs in MC twins. More research is still needed to understand the pathophysiological mechanisms underlying the different incidence of pregnancy complications according to fetal sex and sex pairing among twins.

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Data availability statement. The anonymized datasets generated during and/or analyzed during the current study can be provided on reasonable request.

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Ethical standards. The authors assert that all procedures contributing to this work comply with the ethical standards of the relevant national and institutional committees on human experimentation and with the Helsinki Declaration of 1975, as revised in 2008. The research protocol involved only existing records, based on information routinely collected and stored in a de-identified dataset and hence was considered exempt from ethical review board approval.

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