Is Assisted Reproductive Technology linked to fetal asphyxia? A retrospective Italian case control study.

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Disclosures

The authors declare they have nothing to disclose.

Ethics

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Abstract

Several risk factors are associated with fetal asphyxia. The main aim of this retrospective, analytical, case-control study was to determine whether assisted reproductive technologies (ART) could be considered one of these factors. 162 cases with fetal asphyxia were compared to 361 controls where this event did not occur. We included 32 ART pregnancies, of which 12 obtained through egg donations. 75% (24) of the ART pregnancies experienced fetal asphyxia, suggesting ART increases the risk of fetal asphyxia by about 7 times. This finding is consistent with the literature. The pathogenesis of fetal asphyxia in ART pregnancies is currently unknown. Accordingly, this topic should be further investigated.

Résumé

Plusieurs facteurs de risque sont associés à l'asphyxie fœtale. L'objectif principal de cette étude cas-témoin rétrospective analytique était de déterminer si les technologies de procréation assistée (TPA) peuvent être considérées comme un de ces facteurs. Nous avons comparé 162 cas d'asphyxie fœtale à 361 cas-témoins sans asphyxie fœtale. Nous avons inclus 32 grossesses conçues par TPA, dont 12 conçues par don d'ovules. Dans les grossesses conçues par TPA, l'asphyxie fœtale est survenue dans 75 % (24) des cas, ce qui suggère que les TPA multiplient par 7 le risque d'asphyxie fœtale. Ce résultat concorde avec la littérature. La pathogenèse de l'asphyxie fœtale dans les grossesses conçues par TPA est actuellement inconnue. En conséquence, ce sujet devrait faire l'objet d'autres études.

In 2020 in Italy 11.305 children were delivered thanks to ART , representing 2.7% of live children that were born in the same year .

Infertility is a prevalent disease that affects an estimated 70 million people globally. The World Health Organization estimates that 9% of couples worldwide struggle with fertility issues. ART induced pregnancies have therefore become more frequent due to the large numbers of couples who long for a pregnancy but cannot obtain it spontaneously.

These pregnancies are often considered to have a higher risk of complications as there is evidence they are burdened by an increased risk of preterm delivery, low birth weight, placental abnormalities and stillbirth .

Among the possible complications that may occur during the pregnancy or at birth, we focused on intrapartum asphyxia as is a severe clinical condition that may have very serious long term effects on the newborn child.

We were particularly interested in analyzing possible associations between ART obtained pregnancies and perinatal asphyxia as up to now there is no consistent evidence regarding this association.

Fetal asphyxia is a clinical condition caused by an acute or chronic decrease of maternal and fetal placental gas exchanges, characterized by hypoxemia and hypercapnia, which can induce hypoxic-ischemic encephalopathy, cerebral palsy or death. Cerebral palsy often has no recognizable specific etiology but among the recognized ones we can cite : placental abruption, IUGR, shoulder dystocia, vanishing twin syndrome after I trimester, maternal infection, organizational factors. [1] [2].

Materials and methods

A retrospective observational analytical study was carried out at our teaching Hospital. It is a public, teaching hospital where high-risk pregnancies are referred to from all the region with approximately 2,000 deliveries per year. This study was approved by the local ethics committee.

Our research evaluated a case group of 162 cases of fetal asphyxia registered between 1st January 2010 and 31st October 2019 at our hospital versus a control group of 361 births with no fetal asphyxia. Controls were chosen as consecutive deliveries that occurred on the same day of the cases. Thirty-two ART obtained pregnancies were included in this study.

Fetal asphyxia was identified using the Cerebral Palsy Task Force criteria: Apgar score < 4 at 5th minute, pH < 7, base excess >-12 mMol/L measured on the funicular artery at birth.

The inclusive criteria for the two groups were: single pregnancy, fetus in vertex presentation, gestational age between 37 and 41 weeks and 3 days, calculated according to the first day of the last menstruation, spontaneous or induced labor, spontaneous, operative vaginal delivery or cesarean section, normal admission test (according to the criteria of the 2015 International Federation of Gynecology and Obstetrics 2015 guideline criteria). [3]

The exclusion criteria were: fetuses afflicted with malformations, genetic and chromosomal abnormalities diagnosed during pregnancy or during the hospitalization of the neonate; planned cesarean sections; administration of general anesthesia or opioids to the mother before giving birth.

The clinical data used for this study were obtained from maternal and neonatal medical records, obstetric and neonatal hospital discharge summaries, and birth assistance certificates from the hospital information system. BMI was calculated from the weight recorded at the first clinical evaluation during the first trimester. If the first recorded weight was not during the first trimester the patient declared what her weight was at the beginning of the pregnancy.

As part of the hospital protocol, each labor is always recorded on a partograph.

We consider ‘high activity days” when 9 or more births occur in 24 hours (when the number of births exceeds the hospital-specific 75th percentile of the daily delivery volume).

Statistics

Prepartum and intrapartum variables were considered and analyzed using Fisher test, U Mann Whitney test and logistic regression. The association probability was estimated by the odds ratio with a confidence interval of 95%. An alpha level of 0.05 was considered significant. R Pearson and Spearman's correlation are provided in the result section.

Results

We evaluated the main characteristics of women who underwent ART procedures to obtain a pregnancy (Table 1).

There was no difference between the two populations regarding: ethnicity, smoking, the number of clinical checks and the esteemed fetal growth.

There was also no difference when considering hypertensive disorders, anemia, gestational diabetes, thyroid disease, obstetric cholestasis, premature membrane rupture, and the positivity of the vagino-rectal swab for S.Agalactiae.

As expected, there were more women older than 35 years of age in the ART group ($p<0.001$)(0.252, 0.252) more nulliparous women ($p<0.001$) (-0.140 , -0.140) and a larger number of patients with BMI >35 ($p<0.001$) (0.173 , 0.173).

ART obtained pregnancies were also characterized by a larger number of fetuses with a reduced amniotic fluid index. (p 0.017) (0.106 , 0.106).

When considering the intrapartum variables, ART obtained pregnancies underwent more inductions (p: 0.015) (0.107 ,0.107) and required more often epidural analgesia in labor (p: 0.044) (0.112 , 0.112).

In the ART group there was a higher incidence of abnormal CTG (cardiotocography) traces (p: <0.001) (0.198 , 0.198) and a larger number of cesarean sections (<0.001) (0.159 ,0.150). They also had a higher incidence of meconium tinted amniotic fluid (0.03) (0.095 , 0.095).

There were no differences when regarding: the partograph, the duration of the expulsive period, the neonatal weight at birth, the maternal position at delivery, the incidence of shoulder dystocia and of fever during labor (Table 2).

We also considered the organizational variables: ART-obtained pregnancies were offered less one-to-one care in labor (0.015) (-0.106 , -0.106) and they delivered more often during days of high activity (0.015) (0.090 , 0.090); instead there was no difference in time of birth and day of delivery.

In our study ART almost doubles the risk of developing fetal asphyxia (<0.001) (0.243, 0.243). Furthermore, we stratified to understand whether a specific ART technique individually increased the risk;

heterologous fertilization (<0.001) (0.161, 0.161) and ICSI (Intracytoplasmic Sperm Injection) (0.001) (0.148 ,0.148) were found to be statistically significant in increasing the risk of fetal asphyxia (Table 3).

Discussion

IVF has been correlated with an increased risk of preterm birth (PTB), small for gestational age (SGA) neonates, and pre-eclampsia, all hallmark for placental disorders of pregnancy [4].

Moreover, these pregnancies have a higher incidence of placental abnormalities, so it may be biologically plausible to consider this feature as part of the mechanism involved in perinatal asphyxia.

As previously hypothesized by Delle Pianeet al., in IVF pregnancies a suboptimal placentation implies that offspring were likely to be born with lower birth weight and high placental index [5]. Furthermore, the same study group argued that the increase in placental index in IVF births was an attempt to compensate for impaired function, also indicated by reduced glucose transporter gene transcripts [6]. Hence, the placental index could be a sign of placenta adaption.

When considering fetal asphyxia, there is scarce and often not consistent literature on evidence of an association between fetal asphyxia and ART obtained pregnancies [7] [8].

In some studies the increased incidence of fetal asphyxia and cerebral palsy is attributed to the higher incidence of preterm deliveries and of twin pregnancies in ART gestations [9], this is a strength point of our study because they were excluded from the study sample to avoid possible bias.

Regarding the higher incidence of perinatal asphyxia in the ICSI and heterologous fertilization group, there is little evidence regarding this specific outcome. Some authors suggest that the etiology of infertility may influence the obstetric outcome [10] therefore, different ART techniques may be linked to some specific risk.

Strengths and limitations

This study has some limitations: it is a monocentric, retrospective research with an incrementable sample size.

The strength of this pilot work is the precise focus on ART induced pregnancies and asphyxia, a current topic that needs to be further investigated, with poor current literature regarding this topic.

Conclusions

Further research is needed to understand the possible correlations between neonatal asphyxia and ART pregnancy, in order to stratify the risk for fetal asphyxia and to take it into account when deciding which technique should be used for that specific patient .

This will allow to personalize clinical checks, the timing of the delivery as well as the intrapartum monitoring.

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Tables

Table 1. Prepartum Characteristics

VARIABLE	**CATEGORY**	**ART YES N (%)**	**NO ART (%)**	**C.I 95%**	**P-VALUE**
Age	<35	12 (46.2%)	246 (83.1%)	**0.72-2.75**	**<0.001**
	>35	14 (53.8%)	50 (16.9%)		
Etnicity	European	27 (84.4%)	399 (81.4%)		0.678
	Other than European	5 (15.6%)	91 (18.6%)		
Parity	Nulliparous	28 (87.5%)	290 (59.1%)	**(-2.7)-(-0.185)**	**<0.001**
	Multiparous	4 (12.5%)	201 (40.9%)		
Body Mass Index	<35	22 (68.8%)	446 (90.8%)	**0.042-2.12**	**<0.001**
	>35	10 (31.3%)	45 (9.2%)		
Smoking	No	28 (87.5%)	457 (93.3%)		0.219
	Yes	4 (12.5%)	33 (6.7%)		
Asphyxia	yes	8 (25%)	353 (71.9%)	**0.088-3.86**	**<0.001**
	No	24 (75%)	138 (28.1%)		
Prenatal checks	High risk pregnancy	7 (21.9%)	52 (10.6%)		0.051
	Other kinds of antenatal cares	25 (78.1%)	439 (89.4%)		
Number of clinical checks	None	0 (0%)	10 (3.4%)		0.172
	<6	14 (53.8%)	99 (33.4%)		
	6-10	11 (42.3%)	160 (54.1%)		
	>10	1 (3.8%)	27 (9.1%)		
Esteemed fetal growth	AGA	22 (84.6%)	268(90.5%)		0.527
	SGA	4 (15.4%)	24 (8.1%)		
	LGA	0 (0%)	4 (1.4%)		
Hypertensive disorders	no	28 (87.5%)	458 (93.3%)		0.217
	yes	4 (12.5%)	33 (6.7%)		
Gestational Diabetes Mellitus	no	26 (83.9%)	434 (92.3%)		0.096
	yes	5 (16.1%)	36 (7.7%)		
Thyroid disease	no	31 (90%)	457 (95.6%)		0.161
	yes	3 (10%)	21 (4.4%)		

Gravidic cholestasis	no	31 (96.9%)	483 (99%)		0.282
	yes	1 (3.1%)	5 (1%)		
Amniotic fluid index	Normal	24 (77.4%)	432 (90.8%)	(-1.56)-(0.73)	**0.017**
	oligohydramnios	7 (22.6%)	44 (9.2%)		
	Polyhydramnios	0 (0%)	0 (0%)		
Anemia	no	25 (96.2%)	285 (96.3%)		0.973
	yes	1 (3.8%)	11 (3.7%)		
PROM	no	24 (92.3%)	224 (75.7%)		0.073
	yes	1 (3.8%)	37 (12.5%)		
	>18 hours	1 (3.8%)	35 (11.8%)		
Streptococcus Agalactiae type B positive vaginal swab	no	5 (16.7%)	96 (20%)		0.661
	yes	25 (83.3%)	385 (80%)		

Table 2. Intrapartum Characteristics

VARIABLE	CATEGORY	ART N (%)	NO ART N (%)	C.I 95%	P-VALUE
Type of labour	Spontaneous	17 (53.1%)	359 (73.1%)		**0.015**
	Induced	15 (46.9%)	132 (26.9%)		
Partograph	Normal	24 (75%)	384 (78.2%)		0.884
	Dystocic	7 (21.9%)	83 (16.9%)		
	None	1 (3.1%)	24 (4.9%)		
CTG Trace	Normal	8 (26.7%)	259 (64.4%)	(-1.68)-(1.35)	**<0.001**

	Other than normal	22 (73.3%)	143 (35.6%)		
Type of birth	Eutocic	16 (50%)	371 (75.6%)	(-0.013)-(1.2)	**<0.001**
	Vacuum assisted delivery	2 (6.3%)	36 (7.3%)		
	Urgent cesarean	14 (43.8%)	84 (17.1%)		
Duration of expulsive phase	30 mins- 2 hours	10 (52.6%)	283 (65.2%)		0.641
	>2 hours	4 (21.1%)	25 (5.8%)		
	<30 mins	4 (21.1%)	103 (23.7%)		
Maternal position at birth	Semi-recumbent	5 (27.8%)	100 (23.3%)		0.662
	Other than semi-recumbent	13 (72.2%)	329 (76.7%)		
Neonatal weight at birth (gr)	<2500	3 (9.4%)	31 (6.3%)		0.497
	>2500	29 (90.6%)	460 (93.7%)		
Shoulder distocia	no	31 (100%)	479 (97.8%)		0.497
	yes	0 (0%)	11 (2.2%)		
Amniotic fluid	Clear	22 (68.8%)	410 (83.7%)	(-0.387)-(1.65)	**0.03**
	Meconium	10 (31.3%)	80 (16.3%)		
Fever during labour	no	30 (93.8%)	481 (98%)		0.123
	yes	2 (6.3%)	10 (2%)		
Epidural analgesia	no	8 (30.8%)	152 (51.4%)	(-1.1)-(1.06)	**0.044**

	yes	18 (69.2%)	144 (48.6%)		
One to one care	no	14 (43.8%)	120 (24.4%)	(-0.432)-(1.890)	0.015
	yes	18 (56.2%)	371 (75.6%)		
Time of birth	Day time	20 (62.5%)	274 (55.9%)		0.46
	Night time	12 (37.5%)	217 (44.2%)		
Day of birth	Week day	22 (68.8%)	332 (67.9%)		0.652
	Week -end	9 (28.1%)	121 (24.7%)		
	Bank holiday	1 (3.1%)	36 (7.4%)		
Volume of activity	Medium activity	22 (68.8%)	408 (83.1%)	**(-1.13)-(0.916)**	**0.04**
	High activity	10 (31.3%)	83 (16.9%)		

Table 3. Asphyxia and different ART techniques

VARIABLE	**CATEGORY**	**ASHYXIA**	**NO ASPHYXIA N (%)**	**C.I 95%**	**P-VALUE**
Hormonal stimulation	no	159 (98.1%)	360 (99.7%)		0.056
	yes	3 (1.9%)	1 (0.3%)		
IUI	no	161 (99.4%)	361 (100%)		0.136
	yes	1 (0.6%)	0 (0%)		
IVF	no	159 (98.1%)	358 (99.2%)		0.312
	yes	3 (1.9%)	3 (0.8%)		

ICSI	no	154 (95.1%)	359 (99.4%)	**(-2.297)-2.06**	**0.001**
	yes	8 (4.9%)	2 (0.6%)		
Heterologous Fertilization	no	153 (94.4%)	359 (99.4%)	**(-2.015)-(2.24)**	**<0.001**
	yes	9 (5.6%)	2 (0.6%)		

Abbreviations

IUI: Intra Uterine Injection

IVF: In Vitro Fertilization

ICSI: Intracytoplasmatic Sperm Injection

PROM: Premature Rupture Of Membranes

AGA: Adequate for Gestational Age

SGA: Small for Gestational Age

LGA: Large for Gestaional Age

C.I 95%: 95 % confidence interval