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## Follow-up of children born from assisted reproductive techniques

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### Abstract

Since the introduction of Assisted Reproductive Techniques (ART) in 1978, there has been a notable increase in pregnancies obtained by these methods, mirroring the elevated rates of infertility. Concerns have emerged regarding potential birth complications and cognitive development issues in children conceived through ART. Studies assessing the impact of ART on children have been providing conflicting results, indicating potential predisposition to mental health issues in some cases and no elevated risks in others. These findings have been historically affected by previous policies, particularly those involving the transfer of multiple embryos, leading to a higher occurrence of twin pregnancies. To gather personal perspective, the authors conducted a retrospective observational study at a tertiary center in Oporto, Portugal. Among all children referred to the Neurodevelopment unit from January 1, 2013, to December 31, 2020 (n = 2812), the authors selected 356 children: 298 conceived spontaneously and 58 conceived through ART. A comparison was made between the 298 premature children spontaneously conceived and 43 premature children conceived through ART. Despite ART premature children being more premature than those conceived naturally, no statistical difference was observed in terms of neurodevelopmental disorders, neurodevelopmental delays, or scores on the Griffiths Mental Developmental Scale. Nonetheless, a slight decrease in Griffiths Mental Developmental Scale scores were observed in the ART premature group, alongside lower kindergarten attendance. We anticipate that some of these discrepancies may be attributed to the non-random nature of our sample, as our country lacks a systematic policy for identifying individuals born through ART procedures. In light of these findings, the authors advocate for ongoing surveillance to validate results and address evolving concerns regarding the long-term impact of ART on child development.

**Keywords:** Assisted reproductive techniques, neurodevelopmental disorders, premature, low birth weight, multiple birth offspring, infertility

### Introduction

According to the Central for Disease Control and Prevention (CDC) and the Fertility Clinic Success Rate and Certification Act of 1992, Assisted Reproductive Techniques (ART) encompass a range of fertility treatments involving the manipulation of either eggs or embryos. This process typically entails surgically retrieving eggs from a woman's ovaries, followed by their combination with sperm in a laboratory setting. The resulting embryos are then either reintroduced into the woman's body or donated to others. It is important to note that ART excludes treatments in which only sperm are handled (for example, intrauterine insemination) or procedures in which a woman stimulates their ovaries to produce eggs without the intention of using them afterwards.<sup>[1, 2]</sup>

The first child conceived through ART was born in 1978 in the United Kingdom (UK), and since then there has been an exponential increase in pregnancies by ART, mainly accompanying the increase of infertility rates. According to the World Health Organization (WHO), 1 in 6 people are affected by infertility and it is expected that this trend will continue to rise<sup>[3, 4]</sup>.

As a result of the growing popularity of ART, numerous concerns have arisen regarding children conceived through these laboratory techniques, including potential birth complications [example: premature birth, low birth weight (LBW)], but also the long-term outcomes<sup>[2, 4, 6]</sup>. One of those major concerns revolves around the early development of children,

including their cognitive potential and their alleged risk for neurodevelopmental disorders [2, 4, 7, 8].

Although many studies have been conducted to clarify this correlation, the results have been inconsistent. Svahn *et al.* (2015) concluded that children who are a product of ART tend to suffer from mental health issues such as schizophrenia, mood (affective) disorders, disorders affecting early development, and attention-deficit/hyperactivity disorders [7]. Another study showed a small increase in overall behavioral problems in children conceived through ART at 5 years old (mainly difficulties related to social interaction) [8].

In the opposite direction, some studies have concluded that children conceived through ART do not demonstrate a higher risk of neurodevelopmental disorders when compared to their naturally conceived (NC) counterparts. The same results were reproduced when assessing growth development [2, 9-12].

Many authors have been proposing that the behavioral changes, developmental delays, or cognitive issues observed in children conceived through ART seem to be attributable to medical issues other than ART itself. Obstetric complications and prematurity are frequently referred to the most [4, 5, 9]. Also, it has been suggested that the length of the couple's infertility and the stress associated with its medical treatment could impact the attitudes and expectations of the parents [13]. This may extend to the parent-child relationship, resulting in potential negative behavioral effects and a predisposition to certain disorders [8, 14].

Therefore, this study aimed to evaluate the influence of ART on children's cognitive development using clinical assessment and scores from the Griffiths Mental Development Scale. Secondary goals involved comparing epidemiological, anthropometric, and socio-economic characteristics between children conceived through ART and those NC.

## Materials and Methods

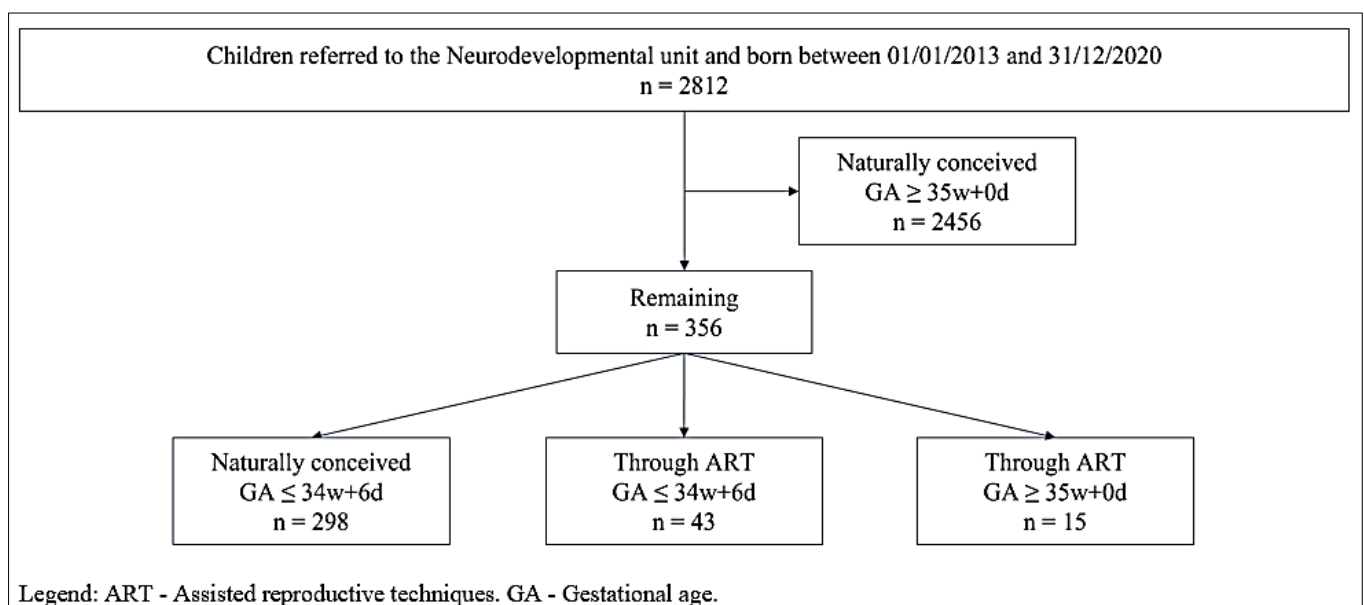
The authors conducted a retrospective observational study at the Neurodevelopment unit of the Paediatric Department of Unidade Local de Saúde São João (ULS São João), Oporto,

Portugal from January 1, 2013, to December 31, 2020. The study was submitted and authorized by the Ethics Committee of ULS São João. Regarding sample selection, it underwent several phases, making it a time-consuming and somewhat challenging process, since those children conceived through ART do not have assigned encoding in the International Classification of Diseases and Related Health Problems – 10th version (ICD10) elaborated by the WHO [15]. This process encompassed, in a first phase, collecting all first referrals to the Neurodevelopment unit during the timeframe of this study; a second phase with a careful review of all clinical records obtained in the first phase, taking into account the inclusion/exclusion criteria; and a third phase with a final review of the clinical records selected in phase two, regarding its division in three main groups: premature children conceived through ART, full-term children conceived through ART and premature children conceived spontaneously.

The inclusion in this study of premature children was a deliberate decision aimed at mitigating potential selection bias. As per protocol at ULS São João, all premature children under 34 weeks of gestation are routinely referred to the Neurodevelopment unit due to their neurobiological risk, even in the absence of developmental concerns. Otherwise, children delivered at term are only referred to the Neurodevelopment unit when they exhibit a deviant neurodevelopmental pattern.

## Inclusion/Exclusion Criteria

Out of all the children referred to the Neurodevelopment unit and born between 01/01/2013 and 12/31/2020 ( $n = 2812$ ), the study included all spontaneously conceived premature children (gestational ages (GA) equal to or less than 34 weeks and 6 days) ( $n = 298$ ) and all children conceived through ART ( $n = 58$ ) either premature (GA equal to or less than 34 weeks and 6 days) ( $n = 43$ ) or full-term (GA greater than or equal to 35 weeks and 0 days) ( $n = 15$ ). Children with GA greater than or equal to 35 weeks and 0 days, conceived spontaneously ( $n = 2456$ ), were excluded from this study (**Fig 1**).



**Fig 1:** Sample selection after application of inclusion and exclusion criteria

### Statistical Analysis

Statistical analysis was conducted using the Statistical Package for the Social Sciences (IBM SPSS Statistics®) version 27, licensed to the University of Porto. The following tests were performed.

- Descriptive analysis using mean and standard deviation, and presentation of frequencies;
- Differences between continuous variables using the Mann-Whitney U test;
- Comparison between frequencies using the Chi-square test;
- Differences with a "p" value less than 0.05 were considered statistically significant.

### Results

The final cohort comprised 356 children: 298 conceived spontaneously and 58 conceived through ART. Among the ART group, 15 were born full-term, and 43 were premature. The study population characteristics are detailed in **Table 1**. In both ART groups, there was a slight male predominance, while no significant sex difference was observed in the NC group. Pregnancies in the premature ART and NC groups were more frequently terminated between 29 and 32 gestational weeks. Median birth weights were 1494 g in the NC group, 1420 g in the premature ART group, and 3112 g in the full-term ART group. Developmental disorders were diagnosed in nearly 30% of the NC group, 20% of the full-term ART group, and almost 70% of the premature ART group. Regarding parental socio-demographic attributes, education levels were apparently comparable across all three groups.

To prevent selection bias, we chose to exclude full-term children conceived through ART from further statistical analysis and only compare the premature groups. **Table 2** presents the comparative results between the NC and premature ART groups. It's important to note that the Griffiths Mental Developmental Scale was not consistently available for all children. Despite the scores in the ART premature group being relatively lower within the study cohort, the observed difference did not reach statistical significance. The ART premature group presented a statistically significant lower mean gestational age and a higher median parental age. Kindergarten attendance was more frequently observed in the NC group (39.9% vs. 30.2% in the premature ART group,  $p < 0.01$ ). There was a higher frequency of twin pregnancies in the ART premature group, although this difference was not statistically significant (19.1% vs. 30.2%,  $p > 0.05$ ). The scores of the Griffiths Mental Developmental Scale were compared between twins and singletons, but the results did not achieve statistical significance. Moreover, singletons were born at lower gestational ages ( $p < 0.01$ ) and spent more days hospitalized at the Neonatal intensive care unit (NICU) ( $p < 0.01$ ).

**Table 3** shows the frequencies of the different ARTs used. *In vitro* fertilization was the most common technique (34; 79.1%).

Refer to **Table 4** for a comprehensive presentation of the pathologies diagnosed during the appointments (exclusively for premature children).

**Table 1:** Description of the study population

	NC (n= 298)	ART full-term (n= 15)	ART premature (n= 43)
<b>Offspring characteristics</b>			
Male   Female - n (%)	149 (50.0%)   149 (50.0%)	8 (53.3%)   7 (46.7%)	25 (58.1%)   18 (41.9%)
Gestational age - n (%)			
22-28 weeks	49 (16.4%)	0 (0.0%)	14 (32.5%)
29-32 weeks	166 (55.7%)	0 (0.0%)	18 (41.9%)
33-34 weeks	83 (27.9%)	1 (6.7%)	11 (25.6%)
35 weeks	0 (0.0%)	14 (93.3%)	0 (0.0%)
Birth weight – median (grams)	1493.8	3112.5	1420.0
Neurodevelopmental disorder - n (%)	89 (29.9%)	3 (20.0%)	30 (69.8%)
Neurodevelopmental delay - n (%)	52 (17.4%)	11 (73.3%)	13 (30.2%)
<b>Parental characteristics</b>			
Paternal education - median	Bachelor	Bachelor	Bachelor
Maternal education - median	Bachelor	Bachelor	Bachelor

**ART:** Assisted reproductive techniques. **NC:** Naturally conceived.

**Table 2:** Comparative results between the NC and ART premature groups

Mann-Whitney U test	NC (n= 298)	ART premature (n=43)	U	p value	
Gestational age - median (weeks)	31	30	5027	<0.05	
Birth weight - median (g)	1494	1420	5838	N.S.	
Griffiths Mental Developmental Scale - median (total quocients)	97	94	2941	N.S.	
Maternal age - median	32	35	6664	<0.001	
Maternal education - median	16	16	400	N.S.	
Paternal age - median	34	38	3779	<0.002	
Paternal education - median	12	12	159	N.S.	
<i>Chi-squared test</i>		NC (n= 298)	ART premature (n= 43)	$\chi^2$	p value
Sex – n (%)					
Male		149 (50%)	25 (58.1%)	0.995	N.S.
Female		149 (50%)	18 (41.9%)		
Gestational age (weeks)					
22-28		49 (16.4%)	14 (32.5%)	6.618	<0.05
29-32		166 (55.7%)	18 (41.9%)		
33-34		83 (27.9%)	11 (25.6%)		

Birth weight (g)				
Extreme low (<1000g)	37 (12.4%)	9 (20.9%)	2.964	N.S.
Very low [1000 - 1500g]	113 (37.9%)	14 (32.6%)		
Low [1500g - 2500g]	143 (48.0%)	19 (44.2%)		
Normal ( $\geq$ 2500g)	5 (1.7%)	1 (2.3%)		
NICU hospitalisation				
Yes	298 (100.0%)	42 (97.7%)	6.904	N.S.
No	0 (0.0%)	1 (2.3%)		
Neurodevelopmental disorder				
Yes	89 (29.9%)	30 (69.8%)	3.561	N.S.
No	209 (70.1%)	13 (30.2%)		
Neurodevelopmental delay				
Yes	52 (17.4%)	13 (30.2%)	0.999	N.S.
No	246 (82.6%)	30 (69.8%)		
<i>Griffiths Mental Developmental Scale</i>				
Very low (<70)	6 (2.8%)	1 (3.0%)	4.907	N.S.
Low [70-79]	8 (3.8%)	3 (9.1%)		
Low average [80-89]	26 (12.3%)	7 (21.2%)		
Average [90-109]	150 (70.8%)	20 (60.6%)		
High average [110-119]	21 (9.9%)	2 (6.1%)		
High [120-129]	1 (0.4%)	0 (0.0%)		
Very high (>130)	0 (0.0%)	0 (0.0%)		
<i>Not evaluated</i>	86	10		
Kindergarten attendance				
Yes	119 (39.9%)	13 (30.2%)	14.833	<0.01
No	179 (60.1%)	30 (69.8%)		

**ART:** Assisted reproductive techniques. **ASD** - Autism spectrum disorder. **NC:** Naturally conceived. **NICU** - Neonatal intensive care unit. **N.S.** - Non-statistical significance.

**Table 3:** Assisted Reproductive Techniques used

	Frequency (%)
<i>In vitro</i> fertilization	34 (79.1)
Intracytoplasmic sperm injection	7 (16.3)
Intrauterine insemination	1 (2.3)
Unknown	1 (2.3)

**Table 4:** Pathologies diagnosed (only for prematures)

	NC (n= 298)	ART premature (n= 43)
Neurodevelopmental delay	52 (17.4%)	13 (30.2%)
Motor delay	16 (5.4%)	3 (7.0%)
Autism spectrum disorder	15 (5.0%)	7 (16.3%)
Cerebral palsy	9 (3.0%)	4 (9.3%)
Chromosomal abnormalities/monogenic disease	15 (5.0%)	4 (9.3%)
Speech disorder	20 (6.7%)	7 (16.3%)
Intellectual development disorder	9 (3.0%)	2 (4.7%)
Attention-Deficit/Hyperactivity Disorder	6 (2.0%)	3 (7.0%)
Specific Learning Disability	5 (1.7%)	1 (2.3%)
Regulatory Disorder	2 (0.7%)	0 (0.0%)

**ART:** Assisted reproductive techniques. **NC:** Naturally conceived.

## Discussion

Our study aimed at assessing the neurodevelopment impact of ART in a cohort of children derived from a Neurodevelopment unit in a tertiary center. From our perspective, this is the first Portuguese endeavour in doing so. The debate around the influence in growth and cognitive development in children conceived through ART is as old as the techniques itself, some of it consumed by the resistance to the novelty [4, 9, 16]. It has been proposed that the manipulation that took place in the laboratory setting could disrupt the normal cell division and differentiation and potentially interfere in the very early embryonic stages [16-18]. Some authors have also suggested an increased occurrence

of congenital defects and/or imprinting disorders (such as Angelman or Beckwith-Wiedemann syndromes) in children conceived through ART compared to the NC ones [17, 19-24].

All these controversies were perpetuated in the literature until the late 1990's through misconstrued studies and a biased group selection [24, 25]. Some of these biases were influenced by the limited relevance attributed initially to obstetric complications (such as LBW and prematurity) in predicting an unfavourable prognosis in ART-conceived children [17, 25-29]. This perspective was moulded by the historical practice of transferring multiple embryos simultaneously, resulting in a higher incidence of twin pregnancies and subsequently higher rates of preterm deliveries [4, 17, 18, 23, 30, 31].

This approach, strongly discouraged in recent decades by numerous scientific societies, has enabled couples to carry out ART pregnancies successfully to full-term. Furthermore, recent efforts undertaken by several developed countries to create national databases, encompassing records of all children conceived through ART, have significantly shaped the discussion concerning the impact of ART on child development [17, 25, 32].

In their 2019 analysis of Finnish records, Goisis *et al.* found that children conceived through ART have a higher risk of adverse birth outcomes. However, they emphasised that this higher risk is largely attributable to factors other than ART itself [5]. Verhaeghe *et al.* (2022) conducted a study including 4349 children born between 24 and 34 gestational weeks from the French prospective cohort EPIPAGE-2, and concluded that there are no discernible differences in cerebral palsy, neurodevelopmental impairment, or developmental coordination disorders between children born through ART and those NC [33]. Analysing data from the UK Millennium Cohort Study, Cozzani *et al.* (2021) found that, despite a higher incidence of LBW among ART children compared to those NC, there is no apparent cognitive development disadvantage [31]. In a similar investigation of



the same UK cohort, Barbuscia *et al.* (2017) determined that ART children tend to achieve slightly better academic scores compared to those conceived naturally [4]. Furthermore, Wang *et al.* (2021), in their examination of the Sweden database, concluded that ART children excel academically beyond their NC counterparts. This achievement is attributed to the fact that, on average, ART children are born to socioeconomically advantaged parents [34]. The researchers also suggested that the higher education level of these parents could potentially mitigate and even reverse some of the disadvantages associated with ART [30, 31, 34, 35].

However, cognitive potential, neurodevelopment, and growth are not the only factors often evaluated. Some studies indicate an increased risk of chronic adult conditions like cardiovascular disease, metabolic syndrome, and cancer in children conceived through ART [9, 23, 36, 37]. Additionally, certain authors suggest a higher risk of mental disorders such as depression, bipolar disorder, and schizophrenia [7-9, 19, 24], and some even suggest an elevated risk for asthma [38]. Conversely, other studies have not found these associations [16, 39-43]. These disparities could be attributed in part to methodological differences among those, encompassing disagreements in defining cases and controls. Furthermore, while some studies examine ART as a unique entity, others distinguish between different types (such as IVF, ICSI, or frozen embryos) or focus exclusively on a specific ART methodology [16-18, 22, 26].

Despite it all, our findings are consistent with the conclusions of the most recent studies [4, 5, 31, 33, 34, 44-46]. Even though our ART premature children being more premature and somewhat lighter than those conceived naturally, we observed no discrepancies in terms of neurodevelopmental disorders, neurodevelopmental delays, or scores on the Griffiths Mental Developmental Scale. Yet, it is important to note that the slightly lower Griffiths scores observed in the ART premature group may be attributed to the non-random nature of our sample. We might be missing ART premature children who weren't referred to our unit by mistake, and there could be cases of children assumed to be NC who were conceived through ART, with that information unavailable in the clinical records, per example, due to parental preferences. Moreover, factors such as limited accessibility may lead many families to choose private health systems for ART treatment instead of public institutions like ours. Consequently, the cases referred to our unit may predominantly involve families relying on the public system for ART access. This could be related to the lower kindergarten attendance observed in our ART premature group, which contrasts with what has been described for ART children in the literature [28, 30]. Nonetheless, consistent with previous studies, we observed that parents of our ART children were older than their NC counterparts [4, 16, 47]. This observation could align with the notion that couples relying on ART may experience delays in accessing treatment. Also, our study did not reveal any predominance of twin pregnancies between groups which aligns with current practices against multiple embryos transfer. Furthermore, singletons were born at a lower gestational age, which explains their prolonged NICU hospitalizations. These findings were unexpected since twin pregnancies typically carry a higher risk of prematurity and, consequently, require longer hospital care [4, 17, 18, 23, 30, 31]. Another limitation of the study was the fact that, given the

variety of ARTs used, it was not possible to compare the results of the Griffiths Mental Developmental Scale according to the technique of conception for the children. ARTs exhibit a wide range of potential genetic manipulation, emphasizing the importance of distinguishing them in future statistical analyses [16-18, 22, 26].

In summary, the evidence for health issues linked to reproductive technology is weak and contradictory, indicating that such associations are unlikely [17]. However, it's crucial to conduct long-term surveillance of children born through ART to confirm and expand on these findings [9, 16, 20, 23-25, 44, 48].

## Conclusion

There is an ongoing debate in the literature regarding the potential impact of reproductive technologies on the growth and cognitive development of children conceived through them. More recent well-designed and thoughtful studies had consistently provided reassurance, denying any inherent association between ART and a higher neurobiological risk. Nonetheless, the authors suggest providing regular medical assessments for children conceived through ART to thoroughly evaluate their long-term outcomes.

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