Effect of medically assisted reproduction (MAR) and pregnancy planning on Bayley-III Screening Test subscales in preterm infants at 12 months of corrected age: a cross-sectional study

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Abstract

Background

The association between medically assisted reproduction and pregnancy planning on overall developmental outcomes of infants has been studied in relatively few studies. The availability of accurate tools for the early detection of developmental delays is a major issue. The purpose of this study is describing the average neurodevelopment of preterm infants and assessing the association between medically assisted reproduction, pregnancy planning and neurodevelopmental outcomes among Hungarian preterm infants.

Methods

Cross-sectional study of preterm infants with low birth weight (< 2500 g) and gestational age < 37 weeks (N = 171) who underwent developmental assessment using Bayley-III Screening Test (Bayley Scales of Infant and Toddler Development Screening Test – Third Edition) in three developmental domains (cognitive, language, motor) at 12 months of corrected age. We examined the developmental pattern of infants and the potential effects of medically assisted reproduction and pregnancy planning on Bayley-III Screening Test subscales. Information on the mode of conception and pregnancy planning was obtained through parental anamnesis.

Results

Concerning developmental delay, the language and motor subscales were the most affected. Examination of the mode of conception and developmental outcomes revealed higher neurodevelopmental skills in infants who were conceived through medically assisted reproduction. Significantly lower cognitive and language skills were found to be associated with unplanned pregnancies. Multi-way analysis of variance was conducted in order to assess the impact of the mode of conception and pregnancy planning on subscales.

Conclusions

We cannot unambiguously conclude that MAR and pregnancy planning had a solely positive effect on the development of preterm and low birth weight infants at 12 months of corrected age, but our results are vital for the design and implementation of further research.

Background

In spite of the development of medical sciences, the number of preterm births is increasing worldwide. Every year approximately 15 million babies are born preterm (before 37 weeks of pregnancy); often

associated with an overlapping perinatal risk, low birth weight (< 2500 g). Preterm birth is not only the leading cause of death among children under the age of 5 [1], but it is responsible for a number of neonatal morbidities that can cause long-term difficulties such as cerebral palsy, vision and hearing impairment, social and emotional problems [2–4]. According to literature findings, preterm infants have significantly lower cognitive, language and motor skills in the early years of life [5, 6].

Higher preterm birth rates and lower birth weight can often be identified in unplanned and children conceived through assisted reproduction [7, 8]. Next to the growing of the levels of involuntary childlessness, the number of babies born after assisted reproductive technologies is currently rising. Since 1978, the birth of the first ART baby, more than 5 million children have been born via ART worldwide [9, 10]. According to the latest ICMART (International Committee Monitoring Assisted Reproductive Technologies) world report, concerning ART treatments, Europe is the most affected, followed by Asia and North America [11]. Assisted reproductive technologies offer a set of techniques (among others e.g. intracytoplasmic sperm injection (ICSI), in vitro fertilization (IVF), frozen embryo transfers) to resolve the problem of infertility and involuntary childlessness [9, 10]. However, there are some common procedures, which cannot be classified into the ART treatments, such as ovulation induction or artificial insemination. This fact necessitated the development of a broader concept, medically assisted reproduction (MAR) [9]. MAR techniques include four main procedures: ovulation induction, artificial insemination, IVF and ICSI [7]. The number of children born after MAR is also high, more than five million [7, 12]. These babies are more exposed to health risks and adverse perinatal outcomes than their naturally conceived peers. Transferring more than one embryo can lead to a higher rate of multiple pregnancies, increased risk of preterm birth and low birth weight [7]. In many cases, the subfertility and advanced maternal age alone can mean a higher risk for worse outcomes [13, 14]. Monitoring and assessment of the developmental differences of these children from naturally conceived peers are essential.

Pregnancy planning is generally related to prenatal and postnatal behaviour of parents [15]. According to the global estimation of Bearak et al. [16], the rate of unplanned/unintended pregnancies was 44% in 2010–2014. These pregnancies can be the consequence of socioeconomic inequality and lead to lower employment resources and education [16, 17]. In case of unplanned, unwanted pregnancies, we often find poorer perinatal outcomes, higher rates of preterm birth, lower birth weight [8], lower paternal support [18] and difficulties in breastfeeding [19]. These factors can directly and indirectly influence the child's development. Kenyhercz et al. [20] highlighted the importance of breastfeeding and positive maternal emotional state before and after birth in the quality of life of 2-year-old preterm children. However, epidemiological research into the association between pregnancy planning and later development of a child is scarce.

The objective of this study:

1. Description of the neurodevelopmental outcomes (cognitive, language, motor skills) of preterm and low birth weight infants at 12 months of corrected age in a Hungarian sample.

2. Examination of the potential influence of medically assisted reproduction and pregnancy planning on neurodevelopmental outcomes of preterm infants at 12 months of corrected age in a Hungarian sample.

Methods

Sample

171 preterm (< 37 weeks) and low birth weight (< 2500 g) children at 12 months of corrected age were examined at the Pediatric Psychology and Psychosomatic Unit of the Department of Pediatrics of the University of Debrecen between December 2017 and May 2019. They underwent developmental assessment using the five subscales of Bayley-III Screening Test. Correction for prematurity was made based on the instructions of the Screening Test Manual [21]. The study was approved by the Medical Research Council of Hungary in compliance with the Ethical Principles of the World Medical Association Declaration of Helsinki. From subjects' parents we asked a written informed consent.

Bayley-III Screening Test (Bayley Scales of Infant and Toddler Development Screening Test – Third Edition)

Developmental psychodiagnostic tools play an important role in the identification of developmental delays. BSID-III (Bayley Scales of Infant and Toddler Development – Third Edition), the advanced version of BSID-II (Bayley Scales of Infant Development – Second Edition), is currently the most advanced and widespread developmental tool for infants and toddlers [22]. Due to its two indices (mental and motor), BSID-II was not able to distinguish developmental delay in the cognitive and language, or the fine and gross motor skills [23]. Development of the Third Edition of Bayley-III was a great leap forward. It measures the early developmental performance of infants and toddlers between 1 and 42 months in five distinct subscales (cognitive, receptive and expressive language, fine and gross motor) [21, 22]. In Hungary, both the diagnostic and screening tests were adapted and standardized in 2017. In our study, we used the Bayley-III Screening Test to determine if the child is developing appropriately or more comprehensive assessment is needed. By administering the Screening Test, degree of developmental delay can be determined: high, moderate and low risk for developmental delays can be distinguished. To classify the performance, the child's total score is compared to given norms. For infants aged 12 months and younger, it takes approximately 15 to 25 minutes to complete [21, 24].

Developmental characteristics; examination of the mode of conception and pregnancy planning

Developmental characteristics (gestational age, birth weight), were obtained from the clinical database of the Department of Pediatrics of the University of Debrecen. Information about the mode of conception (conceived by spontaneous or MAR (ovulation induction, artificial insemination, IVF and ICSI)) and pregnancy planning (planned - unplanned) was obtained based on a maternal anamnesis.

Statistical analysis

Several descriptive statistics were calculated for infants' main characteristics (perinatal and socio-demographic data) and developmental performance. Independent-samples (Student's) t-test was used to compare the means of neurodevelopment of infants conceived by MAR or naturally and planned or unplanned infants. If the standard deviations of the compared populations did not coincide, Welch's t-test was used, instead, as the natural alternative test. In addition, a non-parametric alternative, the Mann-Whitney test, was also carried out to analyse the difference in the distributions of the compared groups. Note that, the latter one is fairly useful in case of smaller sample size. To examine whether mode of conception and pregnancy planning were the most influencing factors for positive or negative changes in cognitive, language and motor development, analysis of variance (ANOVA) was performed with several factors ('multi-way') including possible interactions as well. We tested whether the independent variables in neurodevelopmental outcomes remain significant or not, in addition to other explanatory factors. For all statistical analysis, *IBM SPSS Statistics v25* was used.

Results

Descriptive statistics (mean and standard deviation)

In what follows, notations M, SD and n are used for sample mean, sample standard deviation and sample size, respectively. All infants participating in the study (n = 171) were Hungarian and had valid health insurance. The gender ratio was close to equal, 83 females and 88 males were examined. The mean birth weight of infants was between 260 and 2490 g (M = 1735.56, SD = 579.74). Gestational age of our sample was also low (M = 32.53, SD = 3.27). Main characteristics of our sample are shown in Table 1.

Table 1
Perinatal and socio-demographic characteristics of the overall sample

<i>Perinatal data, n (%)</i>	
Gestational age (weeks)	
very early (< 28 weeks)	20/171 (11.69)
early (28–31 weeks)	29/171 (16.95)
moderate (32–33 weeks)	42/171 (24.56)
late (34–36 weeks)	80/171 (46.78)
Birth weight (g)	
LBW (1500 – 1499 g)	108/171 (63.15)
VLBW (1000–1499 g)	38/171 (22.22)
ELBW (< 1000 g)	25/171 (14.61)
Childbirth	
Sectio caesarea	118/171 (69.00)
Per vias naturales	51/171 (29.82)
<i>Socio-demographic data</i>	
Maternal age at childbirth (years), M ± SD	30.79 ± 6.11
Mother's educational level, n (%)	
Primary	24/171 (14.03)
Secondary technical education	25/171 (14.61)
Secondary vocational education	26/171 (15.20)
Secondary grammar education	19/171 (11.11)
College	38/171 (22.22)
University	33/171 (19.29)
Marital status, n (%)	
Single	9/171 (5.26)
Married	105/171 (61.40)
Cohabiting	39/171 (22.80)
In a relationship	11/171 (6.43)

<i>Perinatal data, n (%)</i>	
Social status, n (%)	
Above-average	68/171 (39.76)
Average	76/171 (44.44)
Below-average	17/171 (9.94)

Neurodevelopmental outcomes on Bayley-III Screening Test Subscales

One of the great benefits of the Bayley-III Screening Test is its ability to predict the risk of developmental delays. It can distinguish high, moderate and low risk for developmental delays compared to levels expected based on their age. In our sample, the proportion of 'high risk for developmental delay' was low, ranging from 0% (cognitive subscale) to 2.92% (expressive language and fine motor subscales). The proportion of 'moderate risk for developmental delay' was slightly higher, ranging from 11.11% (cognitive subscale) to 27.48% (expressive language subscale) (Table 2).

Table 2
Developmental performance on Bayley-III Screening Test subscales (n = 171)

<i>Mean subscale score Developmental delay</i>			
	Mean $\pm$ SD	'High risk for developmental delay', n (%)	'Moderate risk for developmental delay', n (%)
Cognitive Subscale	16.85 $\pm$ 1.45	0/171 (0.00)	19/171 (11.11)
Receptive Language Subscale	11.46 $\pm$ 1.62	4/171 (2.33)	35/171 (20.46)
Expressive Language Subscale	10.84 $\pm$ 1.87	5/171 (2.92)	47/171 (27.48)
Fine Motor Subscale	12.40 $\pm$ 1.55	5/171 (2.92)	34/171 (19.88)
Gross Motor Subscale	15.38 $\pm$ 1.80	4/171 (2.33)	30/171 (17.54)

MAR and neurodevelopmental outcomes

In our sample 47 (27.48%) children were conceived through medically assisted reproduction with 124 (72.51%) infants conceived naturally, without any medical assistance. In 15 cases we did not get any information about the special type of medically assisted reproduction, only ovulation induction (n = 2), artificial insemination (n = 6) and IVF (n = 24) occurred, so we formed an integrated MAR group.

Examining the Bayley-III Screening Test scores, in the group of infants conceived through MAR and naturally, we found that the neurodevelopment of infants conceived by MAR was above average in all

developmental areas compared to naturally conceived peers (Table 3). Significant differences ($p < 0.05$) were found at receptive language and gross motor subscales on both t-tests and Mann-Whitney tests.

Table 3

Comparing the neurodevelopment of infants conceived naturally and by MAR on Bayley-III Screening Test subscales (means, p-values)

	<i>Mean subscale scores</i>		<i>p-values (test statistics)</i>	
	Conceived naturally	Conceived by MAR	Mann-Whitney test p-value (U)	t-test p-value (t)
Cognitive Subscale	16.76	17.10	0.065 (2393.0)	0.172 (1.371)
Receptive Language Subscale	11.26	12.00	0.004 (2096.5)*	0.003 (3.076)*
Expressive Language Subscale	10.70	11.21	0.101 (2449.0)	0.111 (1.603)
Fine Motor Subscale	12.34	12.55	0.320 (2632.5)	0.441 (0.772)
Gross Motor Subscale	15.14	16.02	0.004 (2114.5)*	0.004 (2.893)*
* $p < 0.05$, test statistics (U & t) are given, in case of t-test either the independent sample one or the Welch statistic				

Pregnancy planning and neurodevelopment outcomes

According to the parental interviews, 87.13% of the infants ($n = 149$) were intended pregnancies. We identified unplanned pregnancies in 17 cases (9.94%) and we did not get any information about pregnancy planning in 5 cases (2.92%). Examining the subscales of Bayley Screening Test, planned infants showed higher scores for all variables. The Mann-Whitney test showed significant differences ($p < 0.05$) between planned and unplanned pregnancies on cognitive, receptive and expressive language subscales. T-tests showed similar results, significant differences were identified on the cognitive, receptive language and gross motor subscale levels (Table 4).

Table 4
Neurodevelopmental outcomes of planned and unplanned infants on Bayley-III Screening Test subscales (means, p-values)

	<i>Mean subscale scores</i>		<i>p-values (test statistics)</i>	
	Planned	Unplanned	Mann-Whitney test p-value (U)	t-test p-value (t)
Cognitive Subscale	16.95	16.17	0.027 (861.5)*	0.036 (2.109)*
Receptive Language Subscale	11.63	10.17	0.001 (629.5)*	0.000 (3.623)*
Expressive Language Subscale	10.93	10.05	0.015 (816.5)*	0.069 (1.830)
Fine Motor Subscale	12.46	12.05	0.269 (1063.5)	0.312 (1.014)
Gross Motor Subscale	15.46	14.52	0.089 (956.5)	0.044 (2.029)*
* p < 0.05, test statistics (U & t) are given, in case of t-test either the independent sample one or the Welch statistic				

Other explanatory factors of neurodevelopmental outcomes

ANOVA was used to determine whether pregnancy planning and mode of conception were the most decisive factors or other variables influenced cognitive, language and motor development. We pre-screened those variables that we found relevant and available in this regard, such as gestational age, birth weight, participation in developmental interventions, marital status, mother's educational level, housing, social status and income. Subsequently, the relationship between the pre-screened variables and neurodevelopment was investigated with suitable tests: in the case of nominal variables both with t-tests (as before) and One-Way ANOVA and with their non-parametric counterparts, Mann-Whitney and Kruskal-Wallis tests. For some variables, where there were appropriate scales, the relationship was tested with the existence of a significant correlation. In case of marital status, mother's educational level, housing, social status, and income variables no significant relationship was identified using the Bayley-III Screening Test subscales, so these variables were excluded from further analyses. Five independent variables (factors) (gestational age, birth weight, participation in developmental interventions, pregnancy planning and mode of conception) were considered, which we hypothesized they may influence the neurodevelopmental variables. These five variables were our explanatory factors in ANOVA, such that interactions were also included in the model.

According to the results of ANOVA, no significant effects could be identified on the cognitive or fine motor subscales in case of the five factors. Concerning the receptive language subscale, the pregnancy planning variable had a significant effect ($F = 9.513$, $p = 0.002$). For the expressive language subscale, MAR had a weak, but significant effect ($F = 2.902$; $p = 0.090$) as it can be detected only with a first-order error ($p < 0.01$). Interaction of gestational age with the MAR variable had an effect on the expressive language subscale ($F = 3.491$; $p = 0.017$). Concerning the gross motor subscale, birth weight ($F = 9.352$; p

= 0.000) and pregnancy planning ($F = 6.132$; $p = 0.014$) variables had an independent and joint impact ($F = 2.629$; $p = 0.075$). The mean neurodevelopmental performance of each group is shown in Tables 5–6.

Table 5. Descriptive statistics by gestational age, pregnancy planning and development on Language Subscales: (n), $M \pm SD$

<i>Receptive Language Subscale</i>			<i>Expressive Language Subscale</i>		
Gestational age	Pregnancy planning and participation in developmental interventions (n)	Mean $\pm$ SD	Gestational age	Mode of conception (n)	Mean $\pm$ SD
Late	Planned developed (21) not developed (49)	12.09 $\pm$ 1.33	Late	MAR (21)	11.71 $\pm$ 1.58
		11.02 $\pm$ 1.45		natural (60)	10.61 $\pm$ 2.04
	Unplanned developed (2) not developed (5)	10.00 $\pm$ 1.41	Moderate	MAR (16)	10.12 $\pm$ 1.58
		10.20 $\pm$ 1.64		natural (26)	11.19 $\pm$ 1.38
Moderate	Planned developed (17) not developed (20)	11.41 $\pm$ 1.46	Early	MAR (8)	11.87 $\pm$ 1.12
		11.70 $\pm$ 1.26		natural (20)	10.85 $\pm$ 2.10
	Unplanned not developed (4)	11.00 $\pm$ 0.81	Very early	MAR (2)	12.00 $\pm$ 0.00
				natural (18)	10.11 $\pm$ 1.99
Early	Planned developed (13) not developed (11)	12.38 $\pm$ 2.06			
		11.81 $\pm$ 1.47			
	Unplanned developed (1) not developed (3)	11.00			
		8.33 $\pm$ 1.15			
Very early	Planned developed (13) not developed (5)	11.92 $\pm$ 2.06			
		13.00 $\pm$ 0.70			
	Unplanned developed (1) not developed (1)	12.00			
		10.00			

Table 6
Descriptive statistics by birth weight and pregnancy planning on Gross Motor Subscale: (n) M $\pm$ SD

<i>Gross Motor Subscale</i>		
Birth Weight	Pregnancy planning (n)	Mean $\pm$ SD
ELBW	planned (22)	13.90 $\pm$ 1.23
	unplanned (3)	12.33 $\pm$ 1.52
VLBW	planned (31)	16.00 $\pm$ 1.59
	unplanned (6)	14.00 $\pm$ 2.36
LBW	planned (96)	15.65 $\pm$ 1.72
	unplanned (8)	15.75 $\pm$ 1.66

Discussion

Neurodevelopmental outcomes (cognitive, language and motor)

The Bayley-III Screening Test provides comprehensive information of early childhood cognitive, language and motor development. It is also able to screen children at risk of delayed development, and distinguish high, moderate or low risk for developmental delays. However, the Screening Test does not replace the full BSID-III assessment, based on its results, children cannot be considered to be late in development but only at risk for development delay [21]. In our study, only preterm and low birth weight infants at 12 months of corrected age were examined, we did not have a full-term control group. According to the Bayley-III Screening Test results, receptive, expressive language and fine motor subscales showed the lowest scores and were the most outstanding in terms of risk for developmental delay. This result is consistent with literature findings, regarding preterm infants having significantly lower neurodevelopmental (cognitive, language and motor) skills [25, 26]. Presumably, motor problems negatively affect communication skills, such as face-to-face interaction, joint attention and early linguistic acquisition [25, 6]. Severe or mild mental and neurodevelopmental delay [27], internalising and externalising problems, somatic symptoms [28], behavioural and attention problems, lower academic achievement (mathematics, reading and spelling skills) [29] can be identified in greater proportions of preterm infants in later life. Screening preterm babies at the earliest age, identifying factors that positively or negatively affect their development and initiating early interventions are major aspects of public health.

Mode of conception

Comparing research on the development of infants conceived by assisted reproduction with other research is difficult, not only because of the age of the children involved but also due to the variation of the methodological tools used [30, 31]. According to the systematic review of Bay et al. [32], numerous studies have shown no deficits in neurodevelopmental abilities of children conceived through assisted reproduction compared to naturally conceived counterparts [33–36]. However, there is no complete consensus in the literature. Few studies have identified lower neurodevelopmental performance at 12 and 24 months of age [37, 38], however these findings are discussed. Schendelaar et al. [39] identified better fluency of movements at 24 months of age, while Carson et al. [30] described higher verbal skills of children born after assisted reproduction at 3 and 5 years of age. Concerning cognitive skills, many researchers found no difference in development [31, 40], while others have identified lower developmental outcomes [41, 42]. Based on our study results, infants who were conceived by MAR performed not only similarly but also much better (significantly on the receptive language and gross motor subscales) than naturally conceived children. According to the results of the ANOVA technique, the mode of conception had an independent effect on the expressive language subscale, and we also found explanatory power in interaction with gestational age. We can assume that these children may have experienced greater parental attention and care from the moment of conception; factors that may have contributed to higher cognitive, language and motor development at 12 months of corrected age.

Pregnancy planning

Review of studies about pregnancy planning shows that there is relatively scarce international research where long-term developmental pathways are followed. This line of our research is considered completely groundbreaking in Hungary. Many factors can adversely affect the development of a child born from an unplanned/unintended pregnancy [43]. Carson et al. [30] found that children born of unintended pregnancies have lower verbal skills at 3 or 5 years of age than their planned or artificially conceived counterparts, however this difference was explained by socioeconomic inequalities. In kindergarten, these children show lower social-emotional development [15]. Our results show significantly lower language skills already at 12 months of corrected age, as well as significantly lower cognitive skills. With ANOVA, we examined whether differences in neurodevelopmental performance can be explained by pregnancy planning. In the cognitive subscale, pregnancy planning was not considered significant. In case of the receptive language subscale, pregnancy planning had an independent effect on performance, while in the gross motor subscale birth weight and pregnancy planning had both an independent and interactive effect on the subscale. Although we can identify higher mean scores of planned infants, it cannot be concluded that pregnancy planning is solely responsible for all differences. However, it must be emphasized that pregnancy planning alone had a significant effect on receptive language and gross motor subscales.

Limitations

Potential limitations of our study are the absence of a full-term control group, and the fact the emotions related to conception and time from pregnancy planning to conception were not measured. To overcome these limitations we examine our sample's development with the full BSID-III assessment at the 24 months of corrected age, ask more detailed information about the circumstances of pregnancy planning and gather an adjusted full-term control group.

Conclusions

In terms of neurodevelopmental and intellectual development, preterm children can be regarded as a vulnerable population [28, 27]. Unplanned pregnancies and medically assisted reproduction are often associated with higher rates of preterm births and low birth weight [7, 8]. Cognitive, language and motor screening of children at risk for developmental delay (e.g. children conceived by MAR, preterm and unplanned infants) is essential. Bayley-III Screening Test is an excellent tool for monitoring developmental skills in the early years of life. In addition to providing a complete picture of the child's early cognitive, receptive and expressive language, as well as fine and gross motor skills, it helps to identify problematic areas, making early interventions possible. The potential short- and long-term unfavourable outcomes can be reduced. The significance of our study is increased by the fact it is one of the first pieces of research into preterm infants conducted in Hungary using Bayley-III Screening Test. With our examinations, we wish to promote the importance of early psychological screening. Early detection and treatment of developmental problems can have great benefits not only for the individual but also for society.

Abbreviations

ART: assisted reproductive technology; BSID-II: Bayley Scales of Infant Development – Second Edition; BSID-III/Bayley-III: Bayley Scales of Infant and Toddler Development – Third Edition; ELBW: extremely low birth weight; ICMART: International Committee Monitoring Assisted Reproductive Technologies; ICSI: intracytoplasmic sperm injection; IVF: in vitro fertilization; LBW: low birth weight; MAR: medically assisted reproduction; VLBW: very low birth weight

Declarations

Ethic approval and consent to participate

The study was approved by the Medical Research Council of Hungary in compliance with the Ethical Principles of the World Medical Association Declaration of Helsinki (12053-2/2018/EKU). Informed consent were obtained from parents of subjects.

Consent for publication

Not applicable.

Availability of data and materials

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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Authors' contribution

SzASz and NBE designed the study and drafted the manuscript. SzASz carried out assessments on infants. JMG was responsible for data analysis and helped in writing the manuscript. All authors contributed to interpretation, read and approved the final manuscript.

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Footnotes

Not applicable.

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