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Review article

Assessing the Risk of Cerebral Palsy in Children Born after Assisted Conception – The Role of Multiple Pregnancy and Preterm Delivery

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SUMMARY

For more than three decades, assisted reproductive techniques (ART) have been used as effective treatments to overcome infertility. Since then, numerous studies have been focused on different aspects of long-term health and development of children born after assisted conception. The aim of this paper is to summarize new data on multiple pregnancy and preterm delivery as one of the risk factors which might increase the risk of developing cerebral palsy (CP) in children born after assisted conception.

A comprehensive search of eight databases retrieved 108 papers, 10 of which met inclusion criteria and were relevant for this review.

Despite the dissimilarities in methodological and analytic approaches in the selected studies, *in vitro* fertilization (IVF) and intracytoplasmic sperm injection (ICSI) are generally considered safe, still there is an ongoing discussion whether multiple pregnancy and preterm delivery increase or do not increase the risk of CP in children born after assisted conception.

All information about possible adverse maternal and/or infant outcomes should be made available to the couples seeking ART treatment.

Key words: **assisted reproduction, *in vitro* fertilization, cerebral palsy, disability**

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INTRODUCTION

For more than three decades, since July 25, 1978 when the first baby, Louise Joy Brown, was born after *in vitro* fertilization (IVF) in Great Britain, assisted reproductive technologies (ART) have been used as effective treatments to overcome infertility (1). Since then, more than two million babies have been delivered worldwide through the use of ART procedures (2). *In vitro* fertilization treatment alone now accounts for an estimated 1% of all births in the United States of America (3,4) and 1% to 4% of births in European countries (5) with a proven increase of the percentage of IVF singletons and twins from 1.4% in 1995 to 3.0% in 2000, with an average of 2.3% (6).

Procedures of ART are usually defined as fertility treatments in which both egg and sperm are manipulated in the laboratory, such as IVF and intracytoplasmic sperm injection (ICSI) (7). In both ART treatments, fertilized eggs are implanted after several days of ex vivo cell growth (8). Although ART procedures are increasingly used worldwide over the last decades, there is still concern about the health of the growing population of IVF/ICSI children. The empirical evidences are variable and therefore should be considerably evaluated. Some studies suggested that there were potential difficulties for these children, such as genetic disorders, congenital malformations, preterm delivery, low birth weight and perinatal complications, developmental delays and disabilities, and behavioral and mental health difficulties (1,2,9-15).

Cerebral palsy (CP) is the most common and visible cause of motor disability. Although a decline in the incidence among infants born prematurely was found, the overall prevalence of CP is increasing. This can be explained by the rate of CP that is still stable among term infants, by the increasing survival of preterm and very low birth weight infants, and by the improved longevity in a general population (16,17). Most of the available findings suggest that there is a higher overall risk of CP in the population of children born after ART due to multiple births, preterm (<37 weeks of gestation) and very preterm (<32 weeks of gestation) delivery, low (<2500 g) or very low birth weight (<1500 g) (16-20). Also, these risk factors are strongly associated with numerous long-term health consequences, admission to neonatal intensive care units and prolonged hospitalization (11,21-23). However, multiple ART pregnancies are not considered to be at greater risk of adverse perinatal outcomes than non-ART multiple pregnancies (22). On the other hand, all multiple births are associated with a 4-fold greater risk of CP than singleton births (24). In addition, preterm delivery results in numerous post-partum complications (25,26).

Therefore, the aim of this paper is to summarize new research results on multiple pregnancies and preterm deliveries as one of the risk factors that lead to developing of CP in children born after assisted conception and to systematize evaluated published data of importance for early intervention.

METHODS

An extensive literature search was performed in order to identify relevant studies aimed on detecting the risk factors and determining the incidence of CP in children born after assisted conception. The comprehensive search was performed by using *Google Scholar – Advanced Scholar Search* and limited to articles published since January 1, 1990. The following keywords were used with multiple combinations: "assisted conception", "assisted reproduction", "assisted reproductive technology", "assisted reproductive techniques", "*in vitro* fertilization", "intracytoplasmic sperm injection" (with all of the words) combined with "cerebral palsy" (with the exact phrase). Further, the reference lists of all identified articles were researched for additional relevant studies. The following electronic databases, available through the Consortium of Serbian Libraries for Coordinating Acquisition, were searched using references found by previously strategies: Free Medical, High Wire, EBSCO, Oxford University Press, Cambridge University Press, Science Direct, Wiley Interscience, Directory of Open Access Journals (DOAJ).

As a result of a comprehensive search, a total of 108 studies were collected and examined on the basis of abstract and title; thirty-nine of them met the preliminary inclusion criteria and had the children born after IVF and/or ICSI in their focus. Based on the following criteria, 69 studies were excluded: they were not published in English language, and did not assess neurodevelopmental outcome, i.e. CP. After that, out of the remaining 39 preliminary relevant

studies, 20 were excluded due to inadequate methodological design (review articles, commentaries, editorials, letters, study protocols), and nine of them were focused on children born from donor gametes or children born from surrogate mothers. Therefore, only the remaining 10 studies were analyzed for this study.

RESULTS

There are numerous studies focused on the long-term health and development of children born after assisted conception. Different ART procedures were evaluated in terms of risk factors and possible adverse obstetric, neonatal, cognitive and motor developmental outcomes in these infants. Only a few population-based, cohort studies were aimed at the assessing of the risk factors that lead to developing of CP.

Table 1 shows the summary of studies that investigated associations between assisted conception and CP according to their country of origin, duration, research design, subjects included (number, age, ART method), controlled variables and main conclusions. A summary of estimated risk ratios of CP (both adjusted and not adjusted for preterm delivery and multiplicity) in children born after assisted conception is presented in Table 2.

Table 1. Summary of studies that investigated associations between assisted conception and cerebral palsy

Study (first author, year)	Country, duration	Design	Age	Study group	Control group	Variables controlled for	Main conclusions
Lidegaard, 2005	Denmark, 1995-2001	RPRBC	1–7	6.052 IVF	442.349	Plurality (only sin)	CP rate in IVF sin: 3.3 per 1,000; non-IVF sin: 1.9 per 1,000
Strömberg, 2002	Sweden, 1982-1995	RPRBC	1.5–14	5.680 IVF	15.397	MA, ART procedure, plurality, LBW, PTD, gender, year of birth, birth hospital	After stratification: LBW, PTD, and male sex, not MA, as risk factors
Reid, 2010	Australia, 1991-2004	CC	2–15	1.241 sin IVF/ICSI/GIFT	2.482	Parity, previous miscarriages, gender, GA, birth weight, and weight for GA	No strong association between ART and the risk of CP in sin
Pinborg, 2004	Denmark, 1995-2000	CPRBC	2–7	3.393 tw; 5.130 sin; IVF/ICSI	10.239 tw	Stratification for gender and year of birth	IVF/ICSI tw 3.2, IVF/ICSI sin 2.5, control tw 4.0 (per 1,000); no difference among IVF tw and non-IVF tw, and among ICSI and IVF children
Hvidtjørn, 2006	Denmark, 1995-2000	RPBC	1–7	9.255 IVF	394.713	MA, maternal educational level, parity, plurality, PTD, SGA, gender	PTD (18% of IVF and 5% of non-IVF children)
Hvidtjørn, 2010	Denmark, 1995-2003	PBC	5–13	33.139 IVF/ICSI/OI	555.828	Ma, parity, educational level, smoking, gender, GA, multiplicity	HRR for IVF 2.34 (95% CI: 1.81–3.01); HRR for OI 1.55 (95% CI: 1.17–2.06); multiplicity and PTD as risk factors
Klemetti, 2006	Finland, 1996-1999	RC	2–4	4.559 IVF	26.877	Maternal profession, plurality	Multiple births (35.7% of IVF children and 2.2% of controls)
Ericson, 2002	Sweden, 1984-1997	RPRBC	1–14	9.056 IVF/ICSI	1.417.166	Parity, MA, parental smoking, plurality	Prolonged and more frequent hospitalization of IVF children due to the increased incidence of multiplicity

Zhu, 2010	Denmark, 1997-2003	PBC	5–12	165 with CP; IVF/ICSI	90.203	Waiting time to pregnancy, infertility treatment, MA, parity, smoking, education level, multiplicity and PTD	No significant differences in type and severity of CP between CP cases born after fertility treatment and those born without treatment
Källén, 2010	Sweden, 1982-2007	RPBC	2–17	31.587 IVF	2.623.517	Year of birth, MA, parity, and smoking	CP rate in IVF children: 4.4 per 1,000; OR 0.97 (95% CI: 0.57–1.66) for CP during 2004–2007

Notes: RPRBC - retrospective population registry-based cohort, IVF - *in vitro* fertilization, sin - singletons, CP - cerebral palsy, MA - maternal age, ART - assisted reproductive technologies, LBW - low birth weight, PTD - preterm delivery, CC - case-control, ICSI - intracytoplasmic sperm injection, GIFT - gamete intrafallopian transfer, GA - gestational age, CPRBC - controlled population register based cohort, tw - twins, RPBC - retrospective population based cohort, SGA - small for gestational age, PBC - population based cohort, OI - ovulation induction, HRR - hazard risk ratios, CI - confidence interval, RC - retrospective cohort, OR - odds ratio.

Table 2. Summary of estimated risk ratios of cerebral palsy in children born after assisted conception

Study (first author, year)	Study group	Control group	Estimated risk ratios of CP not adjusted for PTD	Estimated risk ratios of CP adjusted for PTD
Lidegaard, 2005	6.052 IVF	442.349	Sin RR 1.8 (95% CI: 1.2–2.8; p<0.01)	No significant differences in RR of CP in IVF mature sin and IVF premature sin
Strömberg, 2002	5.680 IVF	15.397	All children OR 3.7 (95% CI: 2.0–6.6); sin OR 2.8 (95% CI: 1.3–5.8); tw OR 0.9 (95% CI: 0.4–1.8)	All children OR 2.9 (95% CI: 1.4–6.0); sin OR 2.4 (95% CI: 0.9–6.0)
Reid, 2010	1.241 sin IVF/ICSI/GIFT	2.482	Sin OR 1.19 (95% CI: 0.63–2.24)	Sin OR 0.70 (p=0.367)
Pinborg, 2004	3.393 tw; 5.130 sin; IVF/ICSI	10.239 tw	/	All children OR 0.8 (95% CI: 0.4–1.6); tw OR 0.8 (95% CI: 0.4–1.6)
Hvidtjørn, 2006	9.255 IVF	394.713	All children HRR 1.79 (95% CI: 1.28–2.50); sin HRR 1.28 (95% CI: 0.80–2.03); tw HRR 1.08 (95% CI: 0.57–2.05)	All children HRR 1.07 (95% CI: 0.76–1.52); sin HRR 1.91 (95% CI: 1.00–3.66); tw 1.15 (95% CI: 0.54–2.45)
Hvidtjørn, 2010	33.139 IVF/ICSI/OI	555.828	All children HRR 1.90 (95% CI: 1.57–2.31); sin HRR 1.45 (95% CI: 0.96–2.19); tw HRR 1.08 (95% CI: 0.57–2.05)	All children HRR 0.96 (95% CI: 0.77–1.19); sin HRR 1.21 (95% CI: 0.90–1.62); tw HRR 1.04 (95% CI: 0.71–1.53)
Klemetti, 2006	4.559 IVF	26.877	All children OR 2.92 (95% CI: 1.63–5.26); sin OR 1.15 (95% CI: 0.4–32.7); tw OR 1.52 (95% CI: 0.43–5.4)	88% of IVF children with CP were born preterm
Ericson, 2002	9.056 IVF/ICSI	1.417.166	All children OR 1.69 (95% CI: 1.06–2.68)	/
Zhu, 2010	165 with CP; IVF/ICSI	90.203	All children HRR 3.23 (95% CI: 1.77–5.88)	All children HRR 2.30 (95% CI: 1.12–4.73) +adjusted for multiplicity
Källén, 2010	31.587 IVF	2.623.517	All children OR 1.81 (95% CI: 1.52–2.13); sin OR 1.23 (95% CI: 0.96–1.58); tw OR 0.99 (95% CI: 0.74–1.33)	All children OR 1.05 (95% CI: 0.84–1.53)

Notes: CP - cerebral palsy, PTD - preterm delivery, IVF - in vitro fertilization, sin - singletons, RR - risk ratio, CI - confidence interval, OR - odds ratio, tw - twins, ICSI - intracytoplasmic sperm injection, GIFT - gamete intrafallopian transfer, OI - ovulation induction, HRR - hazard risk ratios.

A study from Denmark (18) was the first systematic register based follow-up study on IVF singletons compared with naturally conceived children. A total of 442.349 non-IVF and 6,052 IVF singletons born in Denmark from January 1, 1995 to December 31, 2001 were included. They were followed during the 7-year study period (mean follow-up time was 4.5 for non-IVF and 4.1 years for IVF group). Twenty of IVF singletons were diagnosed with CP (3.3 per 1.000) and 819 among non-IVF singletons (1.9 per 1.000). This study demonstrated a statistically significant 80% increase in CP in IVF children with a rate ratio (RR) (IVF: non-IVF) of 1.8 (95% confidence interval (CI): 1.2–2.8; p<0.01).

An increased risk of developing CP in children born after IVF compared to matched controls was demonstrated in a population-based retrospective cohort study from Sweden (21). A total of 5.680 children (3.228 singletons, 2.060 twins, 367 triplets, and 25 quadruplets) born after IVF between 1982 and 1995 were included. Two controls were identified and selected for each child giving the total number of 15.397 controls. The authors found almost four-fold increase in all IVF-born children (odds ratio (OR) 3.7, 95% CI: 2.0–6.6) and tripled risk in IVF singletons only (OR 2.8, 95% CI: 1.3–5.8). The most common types found were spastic diplegia, spastic hemiplegia and spastic tetraplegia, followed by ataxic and dyskinetic CP. Stratification by gestational age and birth weight showed still significant increase in risk even in IVF children born after a gestation period of more than 37 weeks (OR 2.5, 95% CI: 1.1–5.2) and in those with a birth weight equal to or greater than 2500 g (OR 2.2, 95% CI: 0.9–5.2). The interpretation of collected data, after stratification, showed that the main risk factors were low birth weight, premature birth, and male sex. Maternal age did not affect the risk. When studied separately, IVF was still an independent risk factor, although not statistically significant. The results showed that there was an increased incidence of twin pregnancies in population of children born after IVF. However, twins born after IVF were at no greater risk of CP than their matched twin controls.

On the other hand, research results of the later Australian study (27) did not confirm findings by Strömberg et al. (21). In their case-control study focused on the risk of CP in singleton children born following ART, Reid et al. (27) found no significant increase in the odds of children with CP being conceived using ART (OR 1.19, 95% CI: 0.63–2.24). ART procedures included IVF, ICSI and gamete intrafallopian transfer (GIFT). However, this study was focused on singleton births only, so the results and conclusion should be interpreted with caution due to exclusion of previously confirmed increased incidence of preterm and multiple births in IVF pregnancies (4,6,16-20,28-31).

In a population-based, controlled national cohort study by Pinborg et al. (32), the main objective was to assess the prevalence rates of neurological sequelae in singletons and twins born following assisted conception compared with naturally conceived twins, and to compare the roles of conventional IVF and ICSI in neurological sequelae in these children. All live-born twins (n=3.393) and singletons (n=5.130) conceived by using ART and naturally conceived twins (n=10.239) born in Denmark between January 1, 1995 and December 31, 2000 were included. The follow-up range was from two to seven years of age. The crude prevalence rates per 1.000 of CP in twins and singletons born after assisted conception and in naturally conceived twins were 3.2, 2.5, and 4.0, respectively. The OR of CP in twins born after assisted conception compared with control twins and adjusted for gender and year of birth was 0.8 (0.4 to 1.6). The corresponding OR for CP in twins after assisted conception compared with singletons after assisted conception was 1.3 (0.6 to 2.9). ICSI children had similar OR for CP as IVF children (0.8, 0.3 to 2.4). According to Pinborg et al. (32), no difference in risk of CP among IVF twins, compared with non-IVF twins, with adjustment for gender, year of birth, maternal age, and gestational age was observed.

A population-based, cohort study from Denmark (6) noted that the higher incidence of preterm deliveries, primarily for IVF twins but also for IVF singletons, represented an increased risk of CP. All live-born singletons and twins born in Denmark between January 1, 1995 and December 31, 2000 were included and followed-up through December 31, 2001 (a range of one to seven years of age). A total of 403.968 singletons and twins were born from 307.960 mothers, and 9.255 (2.3%) of the children were born after IVF from 7.000 mothers. During the follow-up period, 40 IVF singletons and twins (0.43%) and 1.008 non-IVF singletons and twins (0.26%) were diagnosed as having CP (p<0.001). The risk was assessed with a crude hazard risk ratios (HRR) of 1.79 (95% CI: 1.28–2.50). The results

remained largely unchanged with a crude HRR of 1.61 (95% CI: 1.13–2.30), after adjustment for maternal age, educational level, parity, child gender, and small-for-gestational age status. The independent effect of IVF disappeared after additional adjustment for multiplicity or preterm delivery. On the other hand, with both multiplicity and preterm delivery included in the multivariate models, preterm delivery still remained strongly associated with the risk of CP. However, the increased risk of CP for IVF children was still lower than the risk found by Strömberg et al. (21). The results showed that the risk for CP for term IVF singletons was HRR 0.84 (95% CI: 0.43–1.63), and for term IVF twins was HRR 0.83 (95% CI: 0.27–2.61). On the one hand, the risk for CP for preterm IVF singletons was HRR 1.91 (95% CI: 1.00–3.66). On the other hand, the risk was HRR 1.15 (95% CI: 0.54–2.45) for preterm IVF twins. The importance of preterm delivery as an independent risk factor for CP was confirmed. The authors (6) highlighted a presence of larger proportion of IVF children born preterm (18%), compared with non-IVF children (5%), rather than a difference between these two groups. In addition, no difference in the risk of CP in IVF twins and their naturally conceived peers was found. The latter finding is in accordance with the previous corresponding studies by Strömberg et al. (21) and Pinborg et al. (32). At the same time, according to Hvidtjørn et al. (6), the overall risk of any neurological sequelae for children born after conventional IVF and ICSI was the same as the one found by Pinborg et al. (32).

These findings were later confirmed in another population based follow-up study (25). Assisted conception, as a term in the broader context, included IVF, with or without ICSI, and ovulation induction (OI), with or without subsequent insemination. All 588.967 children born in Denmark from January 1, 1995 to December 31, 2003 were included; 5.6% of them were born after assisted conception and 0.19% later received a CP diagnosis. Similar subtypes of CP were observed in children with CP born after assisted conception compared to children with CP born after natural conception. The authors highlighted that there was an increased risk of CP in all children born after assisted conception, and in particular IVF, with a crude HRR 1.90 (95% CI: 1.57–2.31) in comparison to children born after natural conception. When subjects were dichotomized into IVF and OI children and then compared with children born after natural conception, the risk was HRR 2.34 (95% CI: 1.81–3.01) and HRR 1.55 (95% CI: 1.17–2.06), respectively. As presented, with both multiplicity and preterm delivery, as the intermediate factors included in multivariate models, the risk of CP in children born after assisted conception vanished. As for IVF singletons, statistically significantly increased risk of CP was not observed (HRR 1.45; 95% CI: 0.96–2.19). The authors concluded that the increased risk of CP in children born after assisted conception was largely associated with multiplicity and preterm delivery.

Using nationwide registries, Klemetti et al. (14) examined the health of IVF children up to four years of age. A total of 4.559 children born after IVF in Finland from 1996 to 1999 were included in this retrospective cohort study. According to the results, it turned out that 35.7% of IVF children and 2.2% of control children were multiple births, and that 88% of IVF children with CP were born preterm. Although the health of multiple births was worse than that of singletons, the health of IVF multiple births was still comparable to the health of control multiple births. The authors demonstrated that IVF children (singletons and multiple births taken together) had a threefold increased risk of CP until the age of 2 years, compared with control children. However, an increased risk for CP among IVF singletons was not observed as in some corresponding studies (21,32). The authors suggested that increased risk for CP in their study could be mainly explained by multiplicity.

Ericson et al. (10) examined the frequency and duration of hospitalization required by infants born after IVF compared with all infants born in Sweden. Information was provided from a nationwide registration of IVF pregnancies from 1984 to 1997 and a nationwide register of all hospitalized patients till the end of 1998. A total of 9.056 live born IVF infants and 1.417.166 non-IVF infants were identified and compared. After stratification for year of birth, maternal age, parity and smoking, statistically significant increased OR of 1.69 were noted for CP (95% CI: 1.06–2.68). Authors concluded that there was a tendency toward an increased hospitalization of IVF children due to the increased incidence of multiplicity.

In a recent study by Zhu et al. (33) an increased risk of CP in children born after IVF/ICSI was confirmed, even after adjustment for preterm birth and multiplicity, with HRR 2.30 (95% CI: 1.12–4.73). Using the data from Danish National Birth Cohort for

period 1997–2003, among 90.203 children (86.223 singletons, 3.834 twins and 95 triplets), the authors identified 165 children diagnosed with CP (0.18%); 145 (0.17%) of them were singletons, 18 (0.47%) were twins and 2 (2.11%) were triplets. No significant differences in type and severity of CP (motor dysfunction and/or intellectual disability) between CP cases born after fertility treatment and those born without treatment were found.

In the largest study (34) so far, an important conclusion was made regarding the presence of CP in children born after IVF. According to the authors, there is an indication that the risk is decreasing during the last few years. This study included all infants born in Sweden from 1982 (since the birth of the first IVF infant) till 2007. Among 2.623.517 children born, 6.225 were diagnosed with CP (2.4 per 1,000). Among 31.587 children born after IVF, 138 (65 singletons, 67 twins and 6 triplets) were diagnosed with CP (4.4 per 1,000). An estimated crude OR of the risk for CP in all infants born after IVF was 1.96 (95% CI: 1.66–2.31) when only adjusted for the year of birth. After adjustment for the year of birth, maternal age, parity, and smoking, the OR for CP after IVF was 1.81 (95% CI: 1.52–2.13), lower and not statistically significant when singletons or twins were analyzed, 1.23 (95% CI: 0.96–1.58) and 0.99 (95% CI: 0.74–1.33), respectively. However, reduced rate of twins born after IVF (<10%) during the last few years of this study (2004–2007) had an impact on presence of CP in this population of children. The results showed that the OR for CP during that period was 0.97 (95% CI: 0.57–1.66). Stratification for preterm delivery resulted in a lower estimated risk of 1.05 (95% CI: 0.84–1.53) without statistical significance.

DISCUSSION

The role of preterm delivery, as the most powerful predictor of CP, still remains topical. Verlaenen et al. (28) found larger proportions ($p<0.01$) of preterm deliveries in singleton pregnancies after IVF and embryo transfer procedures (11.4%) in comparison to the matched controls (1.43%). Preterm birth is slightly more frequent ($p<0.05$) in IVF singletons than in non-IVF singletons, 7.3% versus 5.3%, respectively, according to Westergaard et al. (29). These findings were later confirmed by the other authors. Hvidtjørn et al. (6) found that the incidence of 18% among IVF children compared with 5% among non-IVF children ($p<0.001$), and the incidence among singletons was 6.5% and 3.7%, respectively, ($p<0.001$).

Spasojević et al. (26) examined morbidity and mortality of premature neonates conceived by IVF. The authors retrospectively analyzed history charts of IVF premature neonates treated at the Neonatal Intensive Care Unit from March 1, 2007 to March 1, 2008. A total of 189 premature neonates were treated, and 25 (13.23%) of them were conceived by IVF. Mean gestational age of IVF neonates was 29.46±3.28 gestational weeks (GW), with the largest number of neonates born between 29 and 31.9 GW (48%). One-minute Apgar score was 5.44±2.45, five-minute Apgar score was 7.16±1.92 and birth weight was 1299±484.35 g. From singleton gestations were 48% of IVF neonates, 40% were from twin and 12% were from trigeminal gestations, giving a total of 52% from multiple pregnancies. Spasojević et al. (26) concluded that morbidity and mortality of IVF premature neonates did not differ significantly from that of other premature neonates treated at Neonatal Intensive Care Unit. Prematurity and low birth weight, along with a multiplicity, were noted as important factors in pathology of these neonates.

Numerous studies confirmed that mothers who achieve a pregnancy after ART were on average older and had a lower parity than mothers who naturally conceived their children. The chances of adverse obstetric and neonatal outcome of pregnancies are increasing with age (35). Results of the research published at the end of last century noted a tendency toward a strikingly different age and parity distribution of the women who delivered after IVF when compared to that of the general population (36). The risk ratio of being aged younger than 30 years (stratified for year of birth) was 0.23 (95% CI: 0.22–0.24) and of the pregnancy being the first was 1.49 (95% CI: 1.46–1.53) (36). According to the later findings highlighted by Lidegaard et al. (18), IVF mothers are 3 to 4 years older in comparison to the mothers of non-IVF children. At the same time, of all primiparous women older than 35 years of life, 20–25% are IVF mothers. This age-trend might fully explain a slightly increased frequency of CP in IVF children detected in primiparous women older than 35 years of life. Hvidtjørn et al. (6) also reported that mothers of IVF children were older ($p<0.001$) and were primiparous more often ($p<0.001$). Results found by Squires & Kaplan (2) showed the mean age of 33

years for women undergoing ART versus 27 years for women who conceived naturally. When data from 1982 till 2007 were analyzed, these observations were largely confirmed (34).

Data collected from 20 European national registers were presented in the 10th annual European IVF-monitoring (EIM) report (31). Analyzed results of ART treatments initiated in Europe during 2006 showed that the proportion of singleton, twin and triplet deliveries after IVF and ICSI combined was 79.2, 19.9 and 0.9%, respectively, giving a total multiple delivery rate of 20.8%. The same rate was 21.8% in 2005 and 22.7% in 2004. Although multiple gestations accounted for only 3% of all live births in the United States of America during 2002, they accounted for 17% of all preterm births, 23% of early preterm births, and 26% of very low birth weight infants, according to Van Voorhis (23). This trend was later confirmed by the Society for Assisted Reproductive Technology (4). Of all infants born through ART in the United States of America during 2004, 50% were born in multiple-birth deliveries making this proportion substantially higher than in the general population during the same period. This trend makes ART a major risk for multiple births. At the same time, there is a higher general risk of CP due to higher proportion of multiples in assisted conception (20,27). The results indicated that IVF children were more frequently born from multiple pregnancies ($p<0.001$); 38.6% of them were twins in comparison to 2.7% of the non-IVF children (6). Moreover, 54.5% of CP children born after assisted conception were multiples compared with only 7.2% of the normally conceived children with CP (25).

It is a common practice to transfer two or more embryos during IVF/ICSI which further leads to an increased risk of losing co-embryos during early pregnancy and therefore to a higher rate of "vanishing embryo syndrome" than in spontaneous pregnancies (37). The risk of CP in a twin surviving in utero death of the other twin, mainly during the third trimester, was assessed as a 40-fold increased in the cohort study of all registered twin births in England and Wales between 1993 and 1995 (38). Referring to this finding, Lidegaard et al. (18) suggested that so-called vanishing twins might be the only explanation of the increased risk of CP in IVF singletons. Additional confirmation of this conclusion lies in the fact that no increased risk of CP was assessed in IVF twins as compared with age-matched non-IVF twins (6,21,32,34).

Comparing the outcomes of IVF after fresh embryo transfer from multiple and singleton pregnancies with one another, and with normally conceived control children, D'Souza et al. (9) pointed out that multiple births were, as the outcome of IVF treatment, associated with a preterm delivery, neonatal conditions and disabilities in later childhood, including CP. A total of 278 IVF children (150 singletons, 100 twins, 24 triplets and 4 quadruplets) born between October 1984 and December 1991, and 278 normally conceived control children matched for age, sex and social class (all singletons), were followed up for four years after birth and assessed for neonatal conditions, CP and other disabilities. The results showed that 46% of IVF children were from multiple births, 34.9% were from preterm deliveries, and 43.2% weighed less than 2500 g at birth. In addition, the IVF singletons were on average born one week earlier than normally conceived control children, weighed 400 g less, and had a threefold greater chance of being born by caesarean section. According to the results, 2.1% of IVF children and 0.4% of the controls, all from multiple births, had mild/moderate disabilities, including two children with CP born as triplets (giving the incidence of 0.7%). In other words, there is a greater risk of developing CP in the surviving fetus after in utero death of one of twins or triplets in multiple pregnancies (9). This was confirmed in some later studies (37,38).

Hvidtjørn et al. (37) performed a population-based cohort study and assessed the risk of CP in children born after IVF/ICSI regarding "vanishing embryo syndrome". All live-born children born in Denmark from January 1, 1995 to December 31, 2000 were included and followed up to December 31, 2001. The incidence of CP was increased in the group of IVF/ICSI children born from twin or higher gestations pregnancies, yet resulted with a smaller number of live children born. The authors (37) concluded that there was an association between "vanishing embryo syndrome" and an increased risk of CP; however, it was not statistically significant. In addition, the authors highlighted that none of 492 children born after single embryo transfer was diagnosed with CP, and noted that this might be due to small sample as a limitation of the study. Results of the recent Danish study (25) showed that in the group of 1.042 IVF singletons born after single embryo transfer no children received a CP diagnosis, confirming the previous conclusion (37). At the same time, 21 (0.28%) of 7.438 IVF singletons born after two or more embryo

transfers ("vanishing embryo syndrome") and 954 (0.18%) of 540.662 normally conceived singletons were CP diagnosis, giving a HRR of 0.28 (95% CI: 0.19–0.44) and 0.18 (95% CI: 0.17–0.19), respectively. The authors suggested that lower frequency of two or more embryos transfer since Danish IVF legislation in 1997 and restricting of number of embryos that could be transferred are possible explanations of this trend.

Examining the long-term outcome of 299 children born after IVF in 1990–1995 in Northern Finland in a population-based cohort study, Koivurova et al. (39) did not identify any difference in their psychomotor development during the first three years of life. Psychomotor development was assessed by modified Bayley scales (Bayley Scales of Infant Development – BSID-I & BSID-II; Bayley, 1969, 1993) and compared to 558 matched controls. This study was conducted as a part of the Finnish national screening program at the ages of 12 months, 18 months, 2 years and 3 years. Still, the postnatal health of IVF children was worse and the growth was slower than of control children probably reflecting the problems in the neonatal period. Evaluating neurodevelopmental outcome of children born after IVF and ICSI, Middelburg et al. (40) conducted a systematic review which included nine register-based and 14 controlled studies focused on assessing outcome of neuromotor development, cognition, speech/language and behavior of children born after IVF/ICSI compared to children born after natural conception. Register-based studies demonstrated that IVF/ICSI per se did not increase the risk for severe cognitive impairment (i.e. mental retardation) or neuromotor disability such as CP, but confirmed the impact of risk factors, such as preterm birth, previously associated with both IVF/ICSI and CP. In controlled studies an excess of neurodevelopmental disorders in IVF/ICSI infants was not observed. However, the main limitation of selected studies was evaluation during infancy only. Therefore, assessment of the risk of neurodevelopmental disorders at older ages, such as dyslexia or fine manipulative dyspraxia was excluded. In systematic review published by Hvidtjørn et al (41), the main focus was on the assessing of associations between ART and CP. This study was based on the original data and articles published from January 1, 1996 to April 1, 2008 with a follow-up of 1 year or more. A total of 19.462 children born after IVF were included. By using meta-analysis, the authors showed that an increased risk of CP was associated with preterm delivery in the population of children born following IVF with estimated crude OR of 2.18 (95% CI: 1.71–2.77).

CONCLUSIONS

This systematic review was focused on existing evidence of associations between different procedures of ART, mainly IVF and/or ICSI, and CP. In order to ascertain the risk of developing CP in children born after assisted conception, current evidences regarding multiple pregnancies and preterm delivery as risk factors for adverse neurodevelopmental outcomes and early development were evaluated and discussed. According to the findings, IVF and related ART procedures are generally considered safe. Most studies of early development of children born after ART demonstrated no additional risk for developmental problems.

There are only a few population-based, cohort studies (6, 18 ,21, 25, 32, 33, 37) assessing the risk of CP among children born after assisted conception. The authors revealed between 1.6- and 3.7-fold increased risks of CP in IVF children when compared to naturally conceived children (6, 10, 18, 21, 25, 33, 34). The recent meta-analysis (41) of summarized data on 19,462 IVF children showed an increased risk of CP with estimated crude OR of 2.18 (95% CI: 1.71–2.77). Some studies (10, 18, 21) reported an association between assisted conception and CP, whereas others could not demonstrate such statistical significance (6, 14, 32). According to the regression analysis, the risk of CP in IVF children is largely attributed to a high proportion of multiple pregnancies, low birth weight, and prematurity in this population (6, 14, 21, 25, 41). The selected studies showed inconsistent findings as some found an association between CP and IVF singletons (18, 21) and others did not (6, 14, 25, 27, 34). As for twin pregnancies after IVF, some studies found no difference in the risk of CP between IVF twins and naturally conceived twins (6, 21 ,32, 34). However, the high incidence of preterm deliveries in twin pregnancies after comparing the obstetric outcome with matched controls was confirmed (6,28 - 30). Hvidtjørn et al. (6) found that rate of preterm deliveries among IVF twins was 35.9%, similar to the non-IVF twins (33.6%). At the same time, the estimated risk of CP in IVF twins was similar to the risk of CP in normally conceived twins (6, 14 ,21, 32,

34). Approximately 88% of IVF children diagnosed with CP were born preterm according to Klemetti et al. (14), while Hvidtjørn et al. (6) reported that 59% of the infants with CP were preterm. According to the results of the recent study (25), as to the proportion of preterm delivery in children with CP, 62.9% of them were born after assisted conception compared to 32.6% born after natural conception. As multiple-gestation pregnancy and multiple-birth are both results of multiple embryo transfer and embryo splitting (11), some authors recommend one embryo transfer during IVF as the way of limiting the risk of developing CP (21,25) and a reconsideration of clinical practice, mainly underscoring the importance of minimizing the number of IVF children born preterm as a way to enhance their long-term health (6, 9, 10, 37).

RECOMMENDATIONS

Despite the dissimilarities in methodological and analytic approaches in assessing the role of multiplicity and preterm delivery, there is no substantial evidence that assisted conception per se leads to a higher rate of CP in children born after assisted conception. It is necessary to devote more attention to the short- and long-term outcomes of the growing population of IVF/ICSI children through further clinical and epidemiologic research.

The presented research results summarized in this review are generally reassuring, although there is an ongoing discussion whether multiplicity, preterm deliveries and low birth weight increase or do not increase the risk of CP in children born after assisted conception. Couples undergoing assisted reproduction should be fully informed about various factors that might contribute to the increased risks of different long-term health and development problems in their offspring. Possible adverse maternal and infant outcomes should be also explained, and importance of achieving successful outcome should be discussed.

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Procena rizika od cerebralne paralize kod dece začete vantelesnim oplođenjem – uloga višestruke trudnoće i prevremenog rođenja

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SAŽETAK

Postupci biomedicinski potpomognutog oplođenja efikasno se primenjuju u lečenju neplodnosti već više od tri decenije. Od tada su objavljena brojna istraživanja različitih aspekata dugoročnog zdravlja i razvoja dece rođene iz trudnoća začetih ovim postupcima. Cilj ovog rada bio je da se sumiraju novi podaci o višestrukim trudnoćama i prevremenom rađanju koji mogu da povećaju rizik od razvijanja kliničke slike cerebralne paralize (CP) kod dece rođene iz trudnoća začetih postupcima vantelesnog oplođenja.

Sveobuhvatnom pretragom osam baza podataka preuzeto je 108 radova, od kojih je 10 ispunilo kriterijume za uključivanje i bilo relevantno za ovaj pregled.

Uprkos metodološkim i analitičkim razlikama prisutnim u odabranim studijama, fertilizacija *in vitro* (IVF) i intracitoplazmatsko ubrizgavanje spermatozoida (ICSI) generalno se smatraju bezbednim. Ipak, glavno pitanje koje i dalje preovladava u naučnim diskusijama jeste da li višestruke trudnoće i prevremeno rođenje povećavaju ili ne povećavaju rizik od CP kod ove dece.

Potrebno je da sve informacije o mogućim neželjenim ishodima po majku i/ili dete budu dostupne parovima uključenim u program vantelesne oplodnje.

Ključne reči: **potpomognuta oplodnja, fertilizacija *in vitro*, cerebralna paraliza, ometenost**