IN VITRO FERTILIZATION AND CEREBRAL PALSY: THE PETŐ INSTITUTE EXPERIENCE

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Background: In vitro fertilization (IVF) may increase the risk of future cerebral palsy (CP). Apart from prematurity, the most common risk factors include protracted or precipitate labor, placental abnormalities, infections, lasting mechanical ventilation and multiple pregnancies. Methods: We examined children born from IVS, their handicap, the type of cerebral palsy and compared with children from control population of same age, from the same district. We analyzed both groups according to the factors which co-vary with CP such as multiple births, preterm births, neonatal complications and parents age. Results: The incidence of IVS amongst children with CP was doubled compared with the control kindergarten. All children were born from twin pregnancies. More than 2 embryos were transferred in 64% of cases. In our group, CP was most likely a consequence of an increased risk of neonatal morbidity associated with multiple pregnancies. Conclusion: Our case-series favors a more widespread use of single embryo transfer.

Keywords: cerebral palsy, in vitro fertilization, twin pregnancies, prematurity

Cerebral palsy (CP), a disorder with a prevalence of about 2 /1000 live births causes a lifelong disability with a substantial impact on family life and societal healthcare costs (Rosenbaum et al., 2007; O'Shea, 2008).

In vitro fertilization treatment alone currently accounts for an estimated 1-4% of births in European countries and 1% of US births (Andersen et al., 2007; Wright et al., 2007). In Hungary in 2011 it was 1,26% (http://www.ksh.hu/docs/hun/xstadat_eves/i_wnt001b.html).

Infants born after in vitro fertilization (IVF) according to most studies differ from spontaneously conceived infants in a number of aspects which could increase the risk for future CP and some other developmental disorders: autism, psychomotor retardation, ADHD, developmental learning disabilities (Ericson et al., 2002; Strömberg et al., 2002; Källén et al., 2005; Lidegaard et al., s.n.; Hvidtjørn et al., 2009; Hvidtjørn et al., 2010). In a minority of studies this was not proved, or just the opposite was shown, that

IVF does not increase the risk of CP (Klemetti et al., 2006; Källén et al., 2010).

Twins from assisted conception have a similar risk of neurological sequelae as their naturally conceived peers and singletons from assisted conception. Children born after intracytoplasmic sperm injection (ICSI) have the same risk of neurological sequelae as children born after IVF (Pinborg et al., 2005).

IVS carries a considerable risk for a number of perinatal complications such as multiple pregnancies and vanishing embryo in these pregnancies, preterm births, low birth weight, neonatal complications (Hvidtjørn et al., 2005; Keogh & Badawi, 2006). Multiple pregnancies are considered to be the major risk factor for CP. However, babies born form single pregnancies after IVF also carried higher risk for perinatal complications and had worse outcome in regard of CP as well.

On the other hand in some studies there were no statistical differences or no differences at all regarding the aforementioned issue or even in the work of Skrablin, IVF acted protectively against later CP (Skrablin et al., 2007).

Most of the data come from Scandinavian countries, which have high health standards, good registries and health related documentation.

We do not know whether some other socio-cultural factors may also contribute to the outcome of IVF pregnancies. The Pető Institute cares for children from *6* month to *18* years – being a representative sample for children with different types of CP.

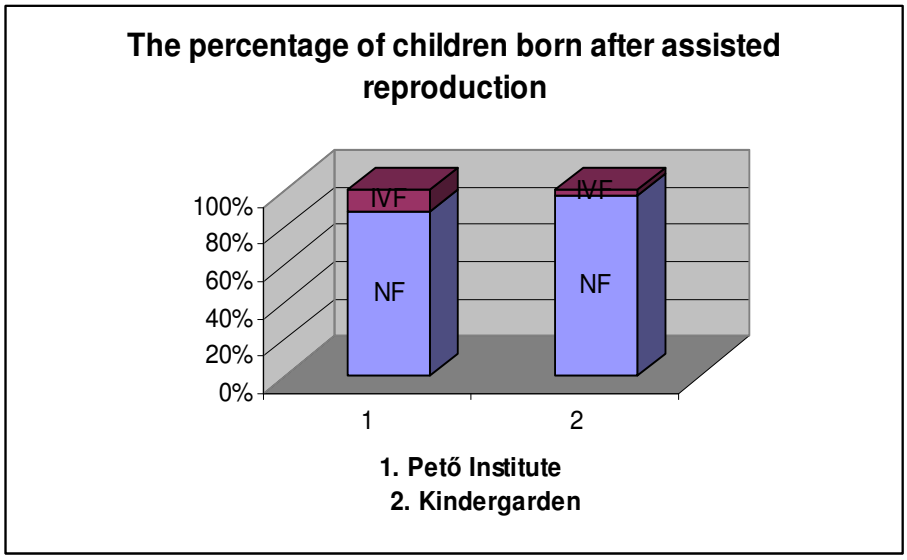
Material and methods.

The study population comprises all children from 3-6 years, attending kindergarten at the Pető Institute (PI) during the school year 2010/211 who had a diagnosis of CP (114 children). Control population were 60 healthy children of the same age, from the same district attending regular kindergarten (KG). We analyzed both groups according to the factors which co-vary with CP such as multiple births, preterm births, type of delivery, Apgar score, maternal and paternal age. Data regarding the IVS are analyzed, (the number of transferred embryos, the number of surviving embryos, data about embryo reductions).

Results

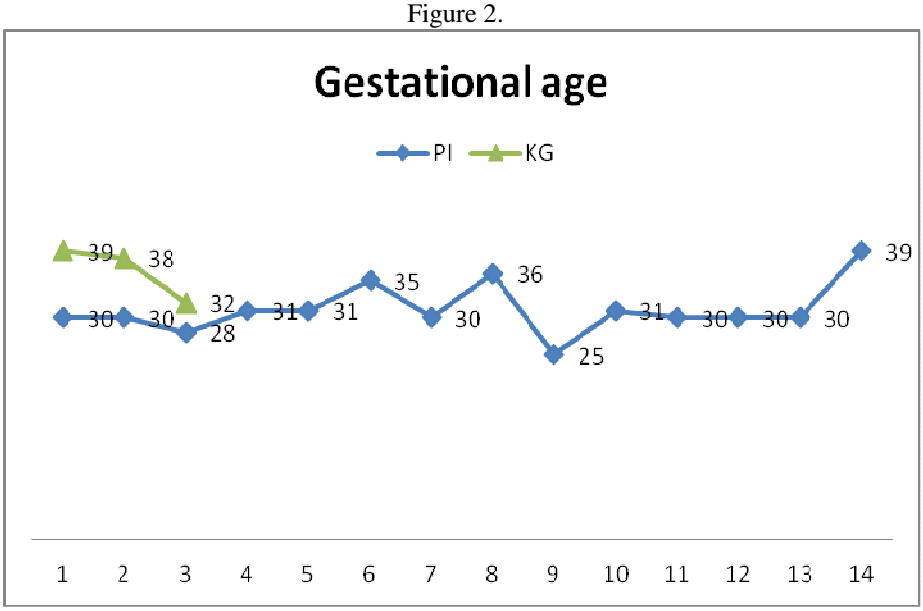
From the 114 children attending kindergarten at Pető Institute who have cerebral palsy we identified 14 children who were born from IF pregnancies (12.3%), one child was conceived after assisted insemination (sperm injection) and was not included into the analysis. In the control group 1 child (1.6%) was born from insemination and 3 (5%) after IVF (Figure 1).

Figure 1.



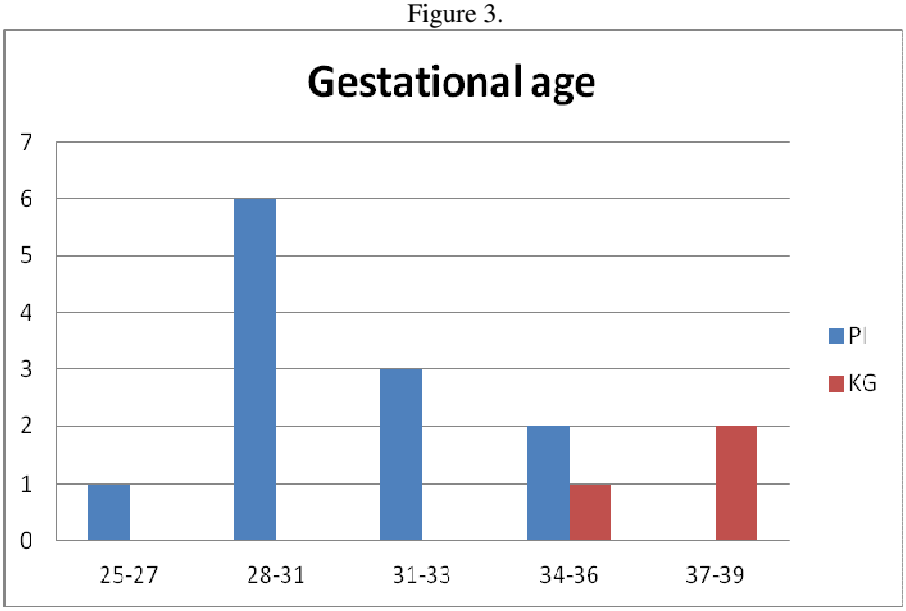
From the children born from IVF, in PI all but one (92.9%) were born preterm (before 37 gestational weeks), in KG only one child was born preterm (25%) (Figure 2). Low birth weight (LBW) (below 2500 g) was present in 12 children (85.7%) in PI - IVF group mean 1415 g, (range: 790-3000 g), from the KG group one child from the IVF conceived children had low birth weight (1900 g).

Figure 2.



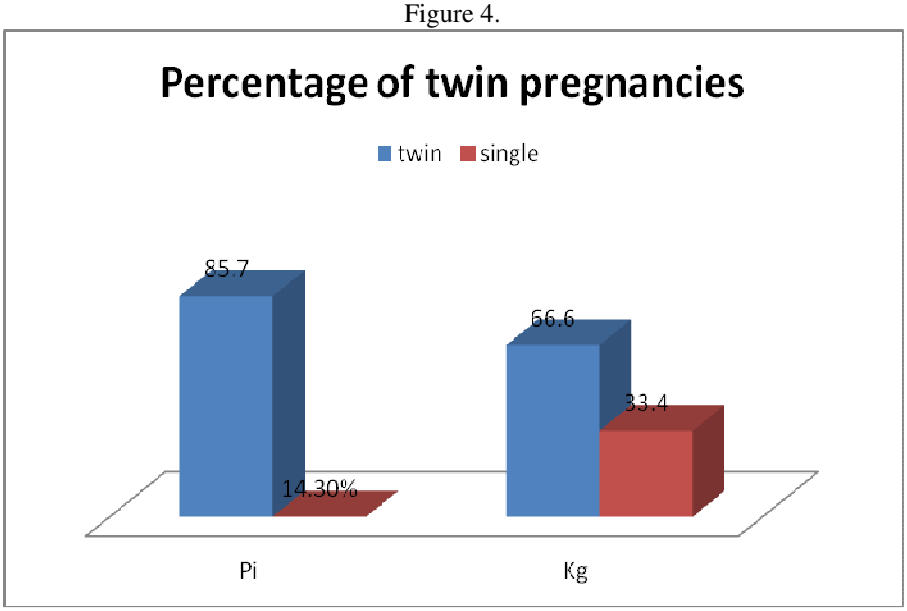
The Apgar scores are shown in the Figure 3, they were lower in the PI – IVR group. All the children from assisted reproduction were born after caesarian section in both groups. There was no case of frozen embryo transfer.

Figure 3.



Multiple pregnancies in IVF babies were present in 12/14 (85.7%) cases from PI and in 2/3 (66.6%) from KG. From PI – IVF children in 4 sets of twins (8 children), both have CP, and both are PI pupils. 3 PI-CP kids have a healthy twin sibling (Figure 4).

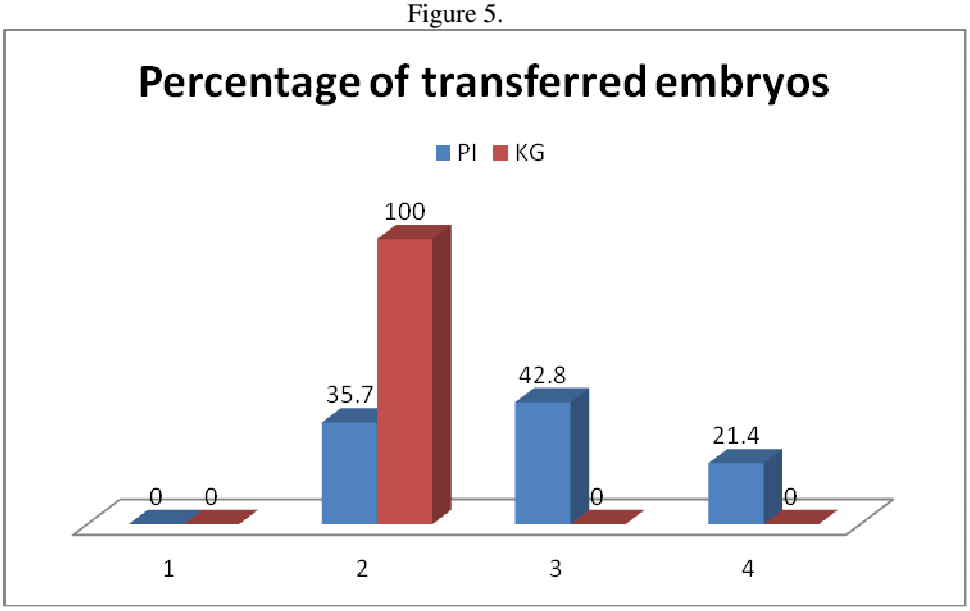
Figure 4.



Six children born from IVF group were born from pregnancies with 3 embryos transferred, 2 pregnancies ended in double (2 twin pairs from PI children), and 2 in a single pregnancy. In three cases, 4 embryos were transferred, in one of them, 3 embryos developed and this triple pregnancy was reduced to double artificially; a selective fetal reduction was performed in order to improve the chances of the remaining fetuses, with one surviving child with CP.

From the 4 transferred embryo group a pair of twins were born (PI – CP group). All the other children were born from pregnancies with 2 embryos transferred (5 children). In the control group only 2 embryos were transferred. In no case was 1 embryo transferred (Figure 5).

Figure 5.



Analyzing the types of CP, they did not differ statistically from other children at the PI. They neither differ in the following co-morbidities: mental retardation (present in 4/14 children at PI), ventriculoperitoneal shunt (present in 3/14 at PI), and epilepsy (present in 3/14 children with CP at PI).

The mean age of the mothers in PI-IVF group was 32.8 y (26-39), of the fathers was 31.6 y (26- 40), (the age of one father was not available). In the control group, mothers were younger; mean: 28 y (27-30), fathers older, mean 33.3 y (28- 40). These differences are statistically not different from the data in the general population.

The time to pregnancy in the mothers of our CP cases was 2.8 years (1-10 y), what is significantly increased compared to the time to the pregnancy reported at healthy children 0.9 y (1-3 y).

The first implantation was successful in PI in 7 cases, only the second was successful in 4 mothers and only the third was successful in 3 mothers,. In the control group, pregnancy followed the first implantation in one, the second in one and the third implantation in one case respectively.

Discussion

The Pető Institute is a representative institution of children with CP in Hungary as about 40% of children with CP get into the purview of conductive education.

Conductive education is an endeavor to enlarge the social environment and to increase the number of social interactions, mostly in group format. Conductive education is a series of actions that activates learning skills and is directed, managed, supported or reinforced by the conductor.

The percentage of IVF-born babies is doubled amongst children with cerebral palsy in PE compared to the control group, where is also high – 5% compared to the national data: 1.26%. This can be explained by the district in which our institute is located; it is a wealthy district of the capital with the oldest population and highest income, where maternal age is higher and women could afford IVF (which is partly privatized) and can reach IVF more easily. We suppose that choosing a rural kindergarten for a comparison would increase the difference. On the other hand, the PI educates children from different parts of Hungary, therefore this selection bias is much lower.

One of the most discussed cause of CP after IVF is the issue of multiple pregnancies. Multiple pregnancies per se increase the frequency of preterm birth, small birth weight, multiple births and vanishing embryo. Most of children with CP were born from double or multiple pregnancies which is the most frequently given explanation for increasing CP risk (Källén et al., 2005; Klemetti et al., 2006; Hvidtjørn et al., 2010). In our small sample, it seems to represent an important risk factor. The vanishing embryo may also play a part in the increased risk according to more recent studies (Pinborg et al., 2005).

We observed that amongst our cases, 3-4 embryo transfers occurred in half of the CP cases. The current professional standpoint is however, that multiple embryo transfer is advocated only under special circumstances.

Because the increased risk of CP in children born after IVF seems to be at least partly connected with preterm delivery, the increased CP risk is associated with multiple pregnancies. In Scandinavian countries the number of embryos transferred is regulated; e.g. in Denmark in 2005 only 1.5% of IVF children were triplets and 32.6% were twins. In contrast, the rate of multiples born after IVF in Hungary is around 5 (Doszpod, 2000; Yael Waknine, 2012).

In Hungary shared financing is applied for IVF. Personal contribution to the costs and often advanced maternal age are urging and motivating factors for a higher number of embryos to be transferred. With the advancement of technical conditions in most cases there would be a good cause for only one embryo to be transferred and thus multiple pregnancies and the increased risk such pregnancies entail could be avoided.

In our cases only the number of transferred embryos is known, not the number of embryos implanted or the gestational age at the time of loss of a co-embryo. The risk of CP in surviving co-embryos has primarily been associated with monochorionicity (Pharoah & Cooke, 1997).

Hvidtjørn et al. found that 3.9 of 1000 (95% CI, 2.2-5.5/1000) singletons born after transfer of more than 1 embryo had CP, so that the vanishing embryo represents also an independent risk factor (Hvidtjørn et al., 2005). Singletons are also more likely to be born preterm and to be of lower birth weight than their naturally conceived counterparts, similarly to twin pregnancies (Jackson et al., 2004) carrying a higher risk of cerebral palsy (Lidegaard et al., 2005). As there was a significant correlation between the development of neurological sequelae and neurodevelopmental diseases and the timing of spontaneous reduction (the later in pregnancy the spontaneous reduction occurred, the higher the risk for CP), the multiplicity of the pregnancies seems to be the key factor. The same study revealed a 1.7-fold increased risk of low birth weight and a 2.3-fold increased risk of very low birth weight in these live-born survivors of a vanished co-twin compared with singletons originating from a single gestation.

The under recognized and underestimated role of genetic factors in development of CP is shown recently. One of the latest “breaking news” in Medscape was exactly this; namely that genetic factors might be the leading cause of CP (Waknine, 2012). The CP rate does not decrease (is constant around 0.2 to 0.3 of live births), despite the enormous development of perinatal intensive care and decrease of perinatal complications and the almost 5-fold increase in the rate of cesarean deliveries performed to avoid difficult deliveries. All children after IVS were born with SC in our sample, so the perinatal damages to the fetus were minimized. So far 6 novel genes have been identified. Genetic screening before IVF could in future probably reduce the risk of CP as well.

Advanced parental age is strongly associated with assisted conception and autism spectrum disorder and learning disability (Hvidtjørn et al., 2010). In a Danish study no significant association between time to pregnancy and the risk of CP was found, whereas children born after IVF had an increased risk of CP (Liang Zhu et al., 2010). An Australian study reported a higher risk of CP among children of subfertile couples who had been registered at an IVF clinic but did not perform the procedure and received no treatment for the pregnancy (Reid, 2010). The time to pregnancy in the mothers of our CP cases was 2.8 years (1-10 y), what is significantly increased compared to the time to the pregnancy reported at healthy children 0.9 y, (1-3 y).

Most studies regarding IVF and CP were conducted in Scandinavia. In Hungary correct CP registry does not exist, and IVF registry works for few years only.

The PI is an Institute with tradition in therapy and education of mentally relatively preserved children with CP. Conductive education is considered as a method of choice to treat CP without mental handicap. Therefore this short case series report excludes more severe forms of CP patients.

There is a rising trend to consider a multiple delivery as a genuine complication of assisted reproduction, which can be prevented by the replacement of one single, selected embryo.

Swedish specialists in reproductive medicine have been in particularly at the forefront of the development of single embryo transfer (denominated SET), which has become the main therapeutic strategy in IVF since 2004. In Sweden, approximately 70% of all treatment cycles with assisted reproduction are now being performed with SET. In Hungary, however, legal restrictions ban the selection of embryos, so that all available embryos (not more than three) are still being transferred.

Providing would-be parents with appropriate information, advising them in detail on possible risks and emphasizing the increased hazard of multiple pregnancies is therefore imperative.

Conclusions: A more widespread use of single embryo transfer would be a balanced cost-benefit intervention to enhance the long-term health of children born after IVF and to rationalize the national costs.

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