# Two histologically different tumours in a neonate born from an assisted reproductive technology pregnancy

## Dwa histologicznie różne guzy u noworodka urodzonego techniką wspomaganego rozrodu

Konefał Halina[1], Peregud-Pogorzelski Jarosław[2], Hnatyszyn Grażyna[1], Posio Viloetta[3], Stepaniuk Maria[4], Kram Andrzej[4], Czeszyńska Maria Beata[1]

[1] Department of Neonatology, Pomeranian Medical University, Szczecin, Poland
[2] Department of Pediatrics, Pediatric Hematology and Oncology, Pomeranian Medical University, Szczecin, Poland
[3] Department of Imaging and Interventional Radiology, Pomeranian Medical University, Szczecin, Poland
[4] Department of Pathomorphology, Pomeranian Medical University, Szczecin, Poland

**Summary**

*The first case of a female neonate born from an in vitro fertilization with embryo transfer (IVF-ET) and intracytoplasmic sperm injection (ICSI) (IVF-ET (ICSI) with two histologically different tumours (craniopharyngioma and hepatoblastoma) is described. Anti-neoplasmatic therapy was abandoned due to the significant extent of the disease (craniopharyngioma, 15×12 cm in diameter with active internal hydrocephalus; and right liver lobe hepatoblastoma, 5 cm in diameter) and the severely impaired general condition of the neonate. The neonate died on the 30th day of life due to cerebellar and brainstem herniation, followed by circulatory and respiratory failure.*

Key words: **newborn** / ***in vitro*** **fertilization** / **craniopharyngioma** / **hepatoblastoma** /

**Streszczenie**

*Przedstawiono Opisano pierwszy przypadek noworodka urodzonego w następstwie zapłodnienia pozaustrojowego (IVF-ET ICSI) z dwoma różnymi histologicznie guzami nowotworowymi (craniopharyngioma and hepatoblastoma). Ze względu na stopień zaawansowania choroby (craniopharyngioma, 15x12 cm z aktywnym wodogłowiem wewnętrznym; hepatoblastoma o średnicy 5,0 cm) i niewydolność wielonarządową po urodzeniu nie podjęto leczenia przeciw-nowotworowego, ograniczono się jedynie do leczenia paliatywnego. Zgon nastąpił w 30 dobie życia, wśród objawów niewydolności oddechowo-krążeniowej.*

Słowa kluczowe: **noworodek** / **zapłodnienie** *in vitro* / **craniopharyngioma** / / **hepatoblastoma** /

**Correspondence to:**
Maria Beata Czeszyńska
Department of Neonatology, Pomeranian Medical University of Szczecin
Unii Lubelskiej St. 1, Szczecin, Poland
tel: +48 607 39 85 27
e-mail: beataces@sci.pam.szczecin.pl

Otrzymano: **25.05.2011**
Zaakceptowano do druku: **16.08.2011**

## Introduction

Foetal and neonatal neoplasms are rare, with an incidence of 1 in 12,000-27,500 live births [1, 2]. Most, but not all, childhood neoplasms occur during the perinatal period [1].

The aetiology of cancer in children is multifactorial, and includes both genetic and environmental factors. The association between congenital abnormalities and tumours is well-established [1, 3]. Certain constitutional chromosome abnormalities specifically favour tumours occurring in the foetal and neonatal periods [2]. Other environmental associations include ionizing radiation, drugs taken during pregnancy, infections, tumours in the mother, and environmental exposure [2]. A number of authors have suggested the possibility of an association between *in vitro* fertilization (IVF) and the presence of some histologic types of tumours in children, such as embryonal and neuroectodermal tumours, neuroblastomas, and retinoblastomas [4, 5]. The advent of foetal ultrasound and magnetic resonance imaging has resulted in more frequent descriptions of antenatal tumours [4, 5]. Brain and liver tumours are among the most frequent neoplasms diagnosed by prenatal ultrasound.

Central nervous system neoplasms comprise the fifth most frequent group of neonatal tumours, as follows: astrocytomas, 36.9%; medulloblastomas, 16%; pineal region neoplasms, 6.7%; neuroblastomas, 6%; craniopharyngiomas, 6%; and ependimomas, 47%. Craniopharyngiomas are benign neoplasms of epithelial origin; however, benign tumours may also be life-threatening because of their size and location [2].

Primary liver tumours comprise approximately 5% of all foetal and neonatal neoplasms. Hepatoblastomas are the most frequent type of liver malignancies in children up to 5 years of age. Less than 10% of tumors present during the neonatal period [6, 7].

The number of children born as a result of advanced hormonal therapy for ovulation and spermatogenesis and assisted reproductive technology (ART) has increased in recent years [8]. Reports on embryonal tumours of the CNS, liver, and bone marrow in foetuses and newborns from ART pregnancies have been reported [4, 9]. Unfortunately, there are no epidemiologic studies which have assessed the risk of neoplasia in foetuses and newborns born from ART pregnancies.

## Case report

A female neonate was born to a healthy 35-year-old mother and a healthy 37-year-old father with no family history of neoplasia. The mother had been treated for several years for infertility. The first IVF attempt resulted in a spontaneous abortion at 8 weeks gestation. The newborn was born from the second pregnancy, which was achieved with IVF and embryo transfer (ET) with intracytoplasmic sperm injection (ICSI). Before and during the ICSI procedure the mother was given the following medications, according to the recommended protocol: Triptorelina, Follitropin recombinant, Menotropinum, Chorionic gonodotropin, Linestrenol, Estradiol, Nadroparine and Acetylosalicylic acid.

At 35 weeks gestation ultrasound and MRI foetal scan revealed the presence of internal hydrocephalus and tumour lesions affecting the entire cerebral hemispheres bilaterally. The foetus was delivered at 37 weeks gestation by caesarean section due to cephalo-pelvic disproportion.

The birth weight was 3550g, the head circumference was 46.5 cm, and the Apgar score at 5 minutes was 6. **A** MRI repeated postnatally confirmed the presence of a 15×12cm cerebral tumour with calcified foci characteristic of a craniopharyngioma (Figure 1A).

The maximum alpha foetoprotein level was 3,184,000 IU/l. The newborn required an incubator environment and passive oxygen therapy.

From the 2nd day of life, an exacerbated jaundice with normal liver function tests. The neonate did not tolerate oral feeding and developed significant abdominal distension. An abdominal ultrasound revealed the presence of a solid, heterogeneous, well-delineated tumour, 5.0cm in diameter, affecting the III and IV segments with an irregular hypoechogenic focus that likely represented necrosis within the tumour (Figure 1B).

A chest X-ray and heart ultrasound were normal. A liver biopsy was not attempted at the request of the parents.

The severe general condition of the newborn and the progressive cardio-respiratory distress were contraindications for chemotherapy. The newborn died on the 30th day of life due to a generalized neoplastic process with symptoms of respiratory and circulatory failure. The autopsy listed the direct cause of death as cerebellar and brainstem herniation. A histopathologic examination confirmed the presence of two histologically different tumours (craniopharyngioma and hepatoblastoma).

On gross examination, the craniopharyngioma occupied the base of the brain and presented as a large, 15 x 12cm cystic tumor. Histologically, squamous epithelium with a palisading arrangement of cells at the periphery of the cell nest was noted. Masses of keratin and calcifications were also present (Figure 2A).

The hepatoblastoma appeared grossly in the liver as a well-defined solid tumor, 5cm in diameter, with areas of necrosis and hemorrhage in the central portion. Microscopically, the hepatoblastoma was composed of immature hepatocytes arranged in irregular laminae two cell layers thick. In some areas, rosettes and a solid or nesting pattern was present (Figure 2B).

## Discussion

We have presented the case of a neonate born following an ART pregnancy with two neoplasms (a craniopharyngioma and a hepatoblastoma) that have no biological link. The published literature with data on the general incidence of congenital tumours is insufficient to calculate the risk of occurrence of such neoplasms in neonates.

Altman et al, published the results of a register-based case-control study that assessed the risk of children with congenital malformations developing cancer [3]. The report confirms that children with congenital malformations have an increased risk of various malignancies. Das et al, indicate a possible association between genetic defects and embryonal neoplasms in foetuses conceived by IVF. In the described case, genetic and congenital abnormalities were not detected [5].

Moore et al, reported that neonatal tumours comprise 2% of childhood malignancies [2]. A review of the literature revealed only 4 cases of neonatal brain tumours in newborns born from IVF pregnancies [5, 9]. Thus far, cases of craniopharyngiomas in children born after natural fertilization have been described [10].

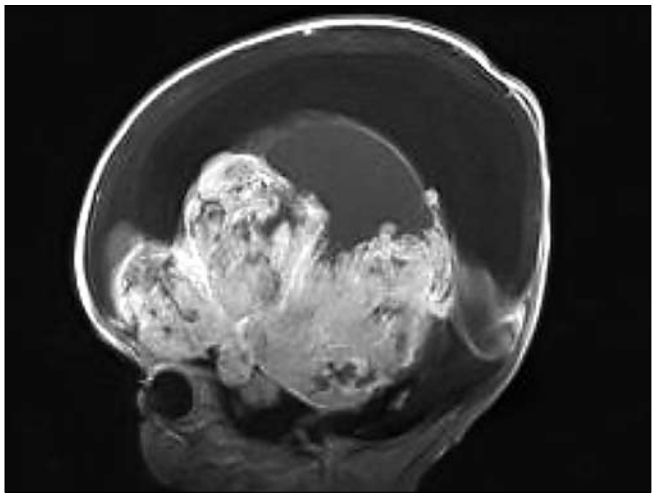

**Figure 1A.** MRI axial post-contrast T1WI shows a large heterogeneous lesion with irregular enhancement. The lesion causes obstructive hydrocephalus involving the lateral ventricles.

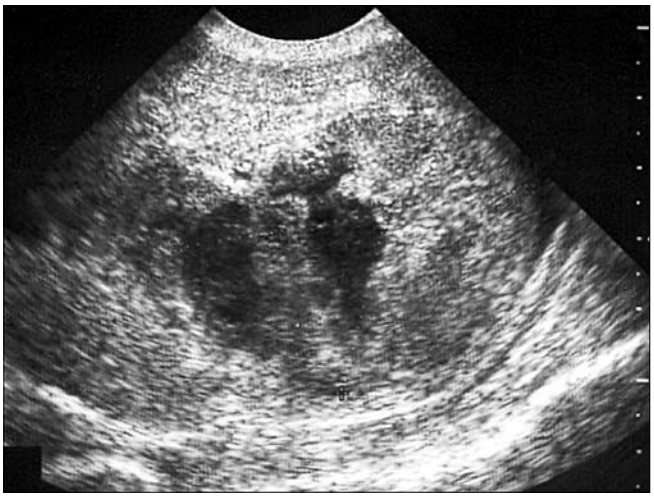

**Figure 1B.** Abdominal ultrasound shows left liver lobe tumour, 5 cm in diameter.

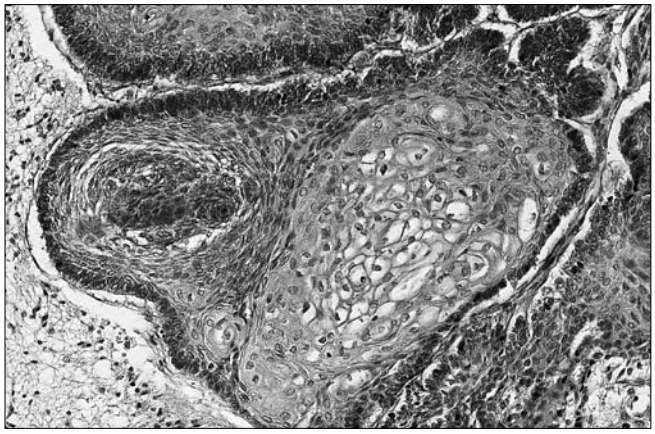

**Figure 2A.** Craniopharyngioma with characteristic palisading of tumor cells (HE stain, original magnification x200).

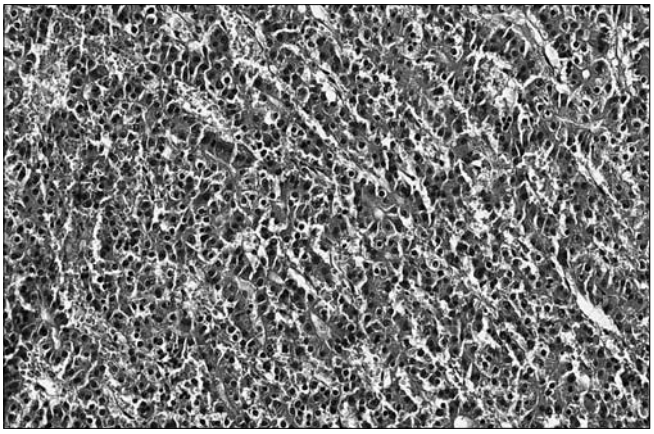

**Figure 2B.** Hepatoblastoma, classical morphology with few rosettes present (HE stain, original magnification x200).

As in our case, one of the patients was not scheduled for surgery due to her serious condition, which is the method of choice in this type of neoplasm [10].

Hepatoblastomas are rare in newborns born from IVF pregnancies [11]. In our case, the hepatoblastoma was not diagnosed during the prenatal ultrasound examination. Moore et al, concluded that majority of tumours with a mass at birth were not identified on antenatal ultrasound [2]. The majority of newborns with hepatoblastomas are scheduled for surgery and chemotherapy [6, 9]; however, it should be emphasized that surgery or chemotherapy are only appropriate for newborns in good clinical condition with small tumours.

We reported a case involving a neonate with two congenital neoplasms born from an ART pregnancy to focus on the precise risk of imprinting and childhood cancer from ART. In recent years, there has been increasing concern regarding the safety of IVF because of the potential health impact on these infants [12]. Kaira and Molinaro, reported an increased risk of congenital and chromosomal anomalies after IVF [12]. The association between IVF and pediatric cancer has been described only in sporadic case reports [4, 5, 9]. Lerner-Geva et al, reviewed the medical records of 332 children from 1254 women who underwent IVF and observed no cancer cases [13]. However, because of the small cohort analysis, a larger prospective study is needed to assess the potential carcinogenic effect on children born after ovulation induction and IVF. Also, Bruinsma et al, who assessed the risk of cancer in 5249 children born after ART at 2 clinics in Victoria, Australia, did not observe a significantly increased incidence of cancer in comparison to the general population [4]. In their study, 4.33 cases of cancer were expected and 6 cases were observed.

Allen et al, searched the Cochrane Library and MEDLINE for English-language articles from 1990-2005 relating to assisted reproduction and perinatal outcomes, and concluded that further clinical research, including long-term follow-up, is urgently required to evaluate the prevalence of imprinting disorders and cancers associated with ART [14]. Raimondi et al, conducted a meta-analysis on 11 cohort studies of ART and subsequent childhood cancer, and concluded that the data are consistent with a lack of increase in risk of childhood cancer, although the amount of data on ART and cancer were limited [15].

In 2009, Felix et al, assessed a pooled analysis of 48 potential sources of data from existing cohort studies of children born after ART [16]. The total number of children enrolled by the studies participating in the pooled analysis was at least 33,981. Their research showed that the current state of data collection in most countries is inadequate to fully address the issue of the long-term safety of ART. The present pooling effort includes expansion of the cohort of children born after ART, updated record linkage for complete cancer cases identification, and calculation of standardized incidence ratios stratified by cause of infertility, socioeconomic status, and hormonal regimen (as well as other confounders) to assess the long-term health status of children born after ART [16]. Thus we conclude, it is time for an epidemiologic study of this issue.

## References

1. Charles A. Congenital tumors. In: Fetal and Neonatal Pathology. Ed. Keeling J, Khong T. London: *Springer-Verlag,* 2007, 327-378.
2. Moore S, Satge D, Sasco A, [et al.]. The epidemiology of neonatal tumours. Report of an international working group. *Pediatr Surg Int*. 2003, 19, 509-519.
3. Altmann A, Halliday J, Gilles G. Associations between congenital malformations and childhood cancer. A register-based case-control study. *Br J Cancer.* 1998, 78, 1244-1249.
4. Bruinsma F, Venn A, Lancaster P, [et al.]. Incidence of cancer in children born after in-vitro fertilization. *Human Reproduction.* 2000, 15, 604-607.
5. Das A, Simmons C, Danielpour M. A congenital brain tumour associated with assisted in-vitro fertilization. Case report. *J Neurosurg.* 2005,103, 451-453.
6. Isaacs H Jr. Fetal and neonatal hepatic tumours. *J Pediatr Surg.* 2007, 42, 1797-1803.
7. Spector L, Johnson K, Soler J, Puumala S. Perinatal risk factors for hepatoblastoma. *BR J Cancer.* 2008, 98, 1570-1573.
8. Bielak A, Hińcz P, Brot A, Wilczyński J. Pregnancy and childbirth course after IVF-ET patients admitted to KMMP IC on Lodz between 1996-2002. *Ginekol Pol.* 2003, 74, 1049-1054.
9. Toren A, Sharon N, Mandel M, [et al.]. Two embryonal cancers after in-vitro fertilization. *Cancer.* 1995, 76, 2372-2374.
10. Kolen E, Horvai A, Perry A, Gupta N. Congenital craniopharyngioma: a role for imaging in the prenatal diagnosis and treatment of uncommon tumor. *Fetal Diagn Ther.* 2003, 18, 270-274.
11. McLaughlin C, Baptiste M, Schymura M, [et al.]. Maternal and infant birth characteristics and hepatoblastoma. *Am J Epidemiol.* 2006, 163, 818-828.
12. Kaira S, Molinaro T. The association of in vitro fertilization and perinatal morbidity. *Semin Reprod Med.* 2008, 26, 423-435.
13. Lerner-Geva L, Toren A, Chetrit A, [et al.]. The risk for cancer among children of women who underwent in vitro fertilization. *Cancer.* 2000, 88, 2845-2847.
14. Allen V, Wilson R, Cheung A, [et al.]. Pregnancy outcomes after assisted reproductive technology. *J Obstet Gynaecol Can.* 2006, 28, 220-250.
15. Raimondi S, Pedotti P, Taioli E. Meta-analysis of cancer incidence in children born after assisted reproductive technologies. *Br J Cancer.* 2005, 93, 1053-1056.
16. Felix A, Bruinsma F, Klemetti R, [et al.]. International pooled analysis of cancer incidence in children after assisted reproductive technologies: interim report. *Future Oncol.* 2009, 5, 901-6.