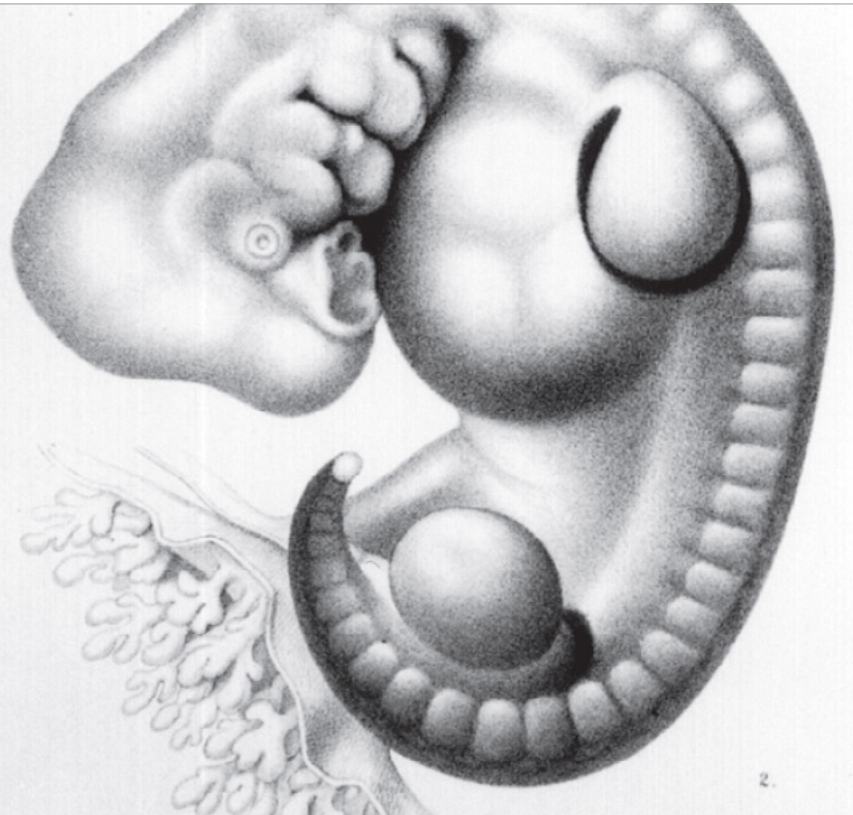
SWISS SOCIETY OF NEONATOLOGY

Fetal retinoid syndrome



May 2016

Claude F, Ferrucci E, Valdo P, Giacchetti L, Department of Pediatrics and Neonatology, Ospedale Regionale di Lugano, Switzerland

Title figure:
Source: Hopwood N. Producing development: the anatomy of human embryos and the norms of Wilhelm His. Bull Hist Med 2000;74:29–79.

Isotretinoin, the most well known retinoid, has been used for treatment of severe cystic and conglobate acne since the 1980s (1). Isotretinoin is a synthetic derivative of vitamin A. It is a teratogenic drug with influence on cell growth and differentiation (2).

Within years of licensing, cases of neonatal malformations were reported when the drug was used just before or during pregnancy (3). These malformations are best known as fetal retinoid syndrome and include pre- and postnatal growth restriction, craniofacial, central nervous system, cardiovascular, thymic, and parathyroid abnormalities or defects (1 – 3). Results of recent animal studies suggest that isotretinoin intake during the first three months of pregnancy can cause hypervitaminosis A, which in turn influences cell phenotype expression through the HOX signaling pathways (involved in branchial arch patterning) and can thus lead to malformations (1, 4).

This female infant was born at 36 5/7 weeks of gestation by normal vaginal delivery. The mother was an 18-year-old G1/P1 with a complex social background. When she first presented to our Department of Obstetrics and Gynecology, she was unaware of her pregnancy, but assessed to be at around 23 weeks of gestation. She failed to keep her regular pregnancy appointments and was eventually admitted in labor at 36 5/7 weeks of gestation for spontaneous vaginal delivery. The girl adapted well with Apgar scores of 5, 6, and 9 at 1, 5 and 10 minutes, respectively. Umbilical arterial cord pH was 7.26.

At birth, she was hypotonic and hyporeactive, with central cyanosis. She required positive pressure ventilation with a T-piece device for two minutes with good clinical response. Her birth weight was 2640 g (P10-25), length 46 cm (P5-10) and head circumference 31.5 cm (P5-10). She was admitted to our neonatal ward for monitoring and clinical observation.

On examination, several facial abnormalities were noted (Fig. 1). There were hypertelorism, elongated palpebral fissures, a depressed nasal root, as well as ptosis of the left eyelid. In addition, micrognathia, thin lips, asymmetric opening of the mouth with deviation to the left and a high arched palate were observed. Finally, dysmorphic and low set ears were present.

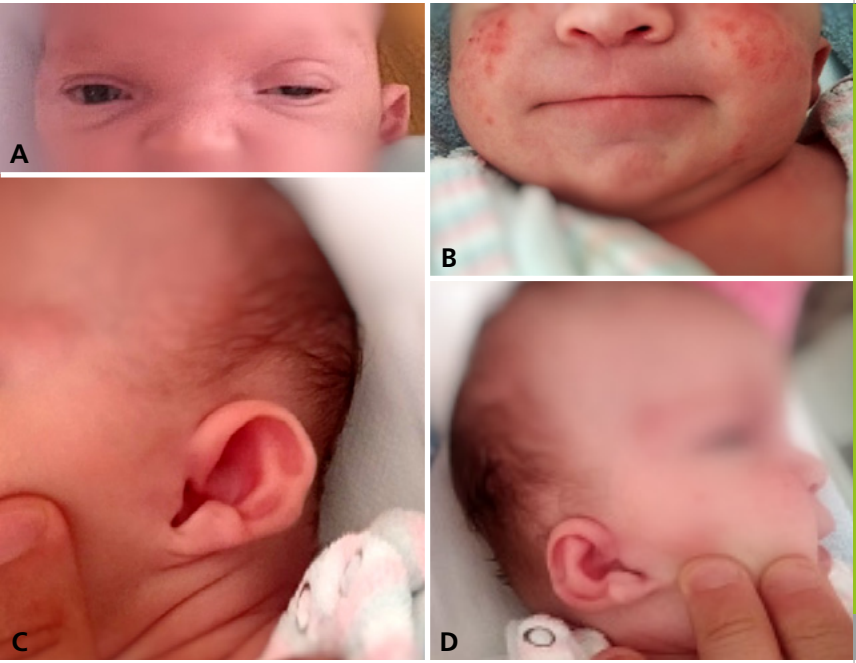


Fig. 1

Facial abnormalities: A) hypertelorism, elongated palpebral fissures, ptosis of left eyelid; B) micrognathia, thin lips C) and D) dysmorphic low-set ears, thin upper lip, depressed nasal bridge.

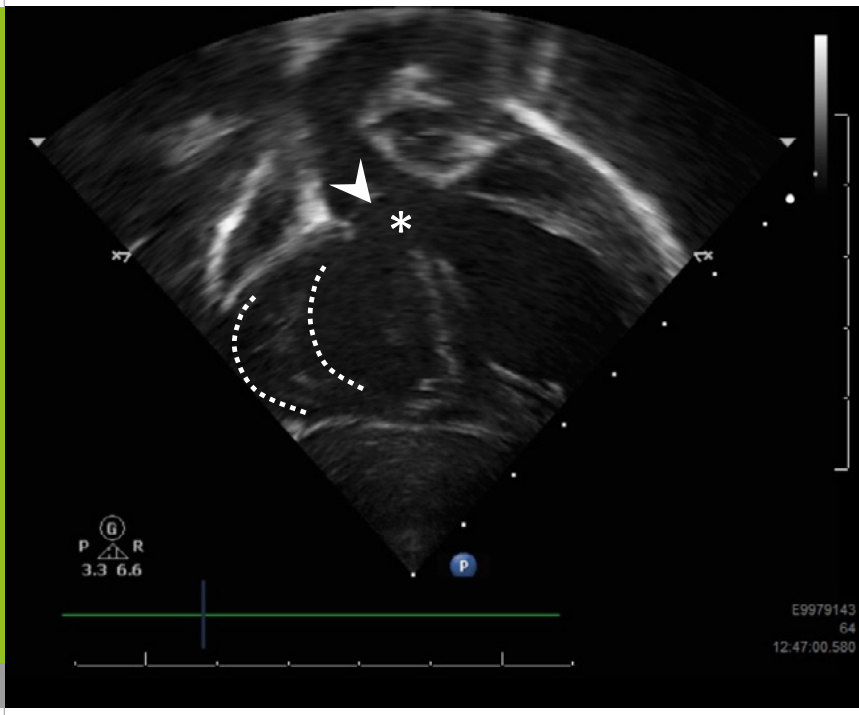


Fig. 2

Echocardiography showing tetralogy of Fallot with ventricular septal defect of 9 × 8 mm (asterisk), right ventricular hypertrophy, (dotted lines) and overriding aorta (arrow head); pulmonary stenosis not seen in this view.

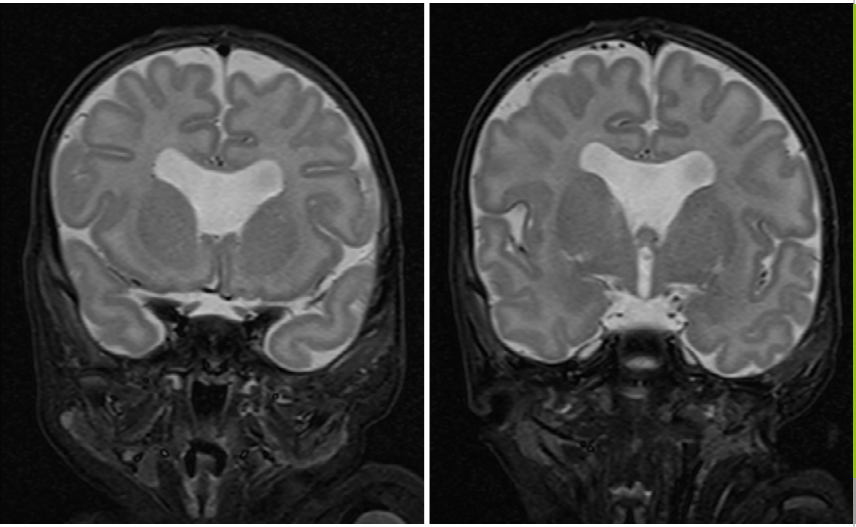


Fig. 3

MRI T2 (coronal view): agenesis of septum pellucidum with low set fornix and enlarged lateral ventricles.

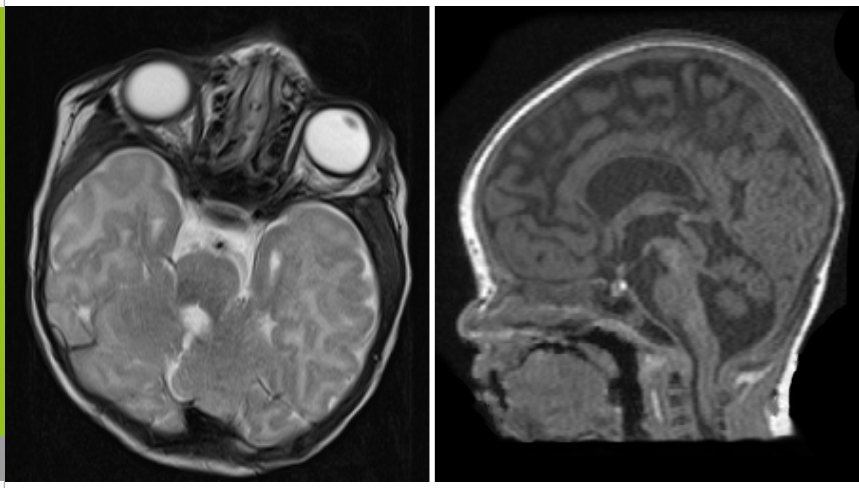


Fig. 4

MRI: A) T2 (horizontal view): aplasia/hypoplasia of cerebellar vernix; T1 (sagittal view): hypotrophic aspect of the cerebral trunk, dysmorphic aspect of midbrain tegmentum and quadrigeminal plate.

She remained hypotonic and poorly responsive to stimuli in the first days of life. She had feeding difficulties with an uncoordinated suck, and frequent episodes of bradycardia and desaturations. A 3/6 systolic murmur was further investigated by ECG and echocardiography; the latter revealed classical tetralogy of Fallot (Fig. 2).

On cerebral ultrasound examination, thinning of the corpus callosum and absence of the septum pellucidum with mild dilatation of the lateral ventricles were noted. These findings were confirmed by MRI (Fig. 3), which also revealed aplasia/hypoplasia of the cerebellar vermis, hypotrophy of the cerebral trunk with a dysmorphic aspect of midbrain tegmentum and quadrigeminal plate (Fig. 4). On polysomnography, there was moderate asymmetry of electrical brain activity without epileptiform discharges.

Karyotype (46, XX) and FISH analysis revealed no chromosomal abnormalities or microdeletion syndromes, such as DiGeorge 22q11. Results of an abdominal ultrasound examination, an ophthalmologic evaluation and otoacoustic emissions (OAEs) were also without abnormalities.

The history of maternal isotretinoin intake during the first three months of pregnancy only became known a few days after delivery; as a consequence, a diagnosis of fetal retinoid syndrome was made.

At the time of this report, the patient is still awaiting definitive cardiac repair; unfortunately, there is evidence of significant neurodevelopmental impairment.

We performed a non-exhaustive review of case reports using the following keywords: «fetal retinoid syndrome», «isotretinoin embryopathy» or «retinoid syndrome». In the last 10 years, eight articles describing a total of ten patients have been published (5 – 12). As in our case, all reported patients presented with various anomalies of the head (head shape, malformed ears, abnormalities of the palpebral fissure, nasal bridge, and lips). A high arched or cleft palate were described in three of the patients (5, 6, 10). Anomalies of the auricles were a common finding (five patients) and associated with malformations or dysfunctions of the external auditory canal, the middle ear, the inner ear or the mastoid (6, 7, 11, 12). Four patients presented with visual impairments (nystagmus, strabismus, anomalies of retina) (5 – 7). CNS involvement was also common with structural anomalies of the cerebellum, the corpus callosum and the cranial nerves. Seizures and muscular hypotonia were common (5 – 8, 10 – 12). Finally, congenital heart disease (ASD, VSD, PDA, aortic anomalies, pulmonary hypertension) was described in five patients (6, 7, 9 – 11).

Strict guidelines must be followed when prescribing isotretinoin to women of childbearing age (1, 3, 13). In Switzerland, physicians must inform their patients about the teratogenic effects of isotretinoin and the necessity of using some form of contraception to prevent pregnancies during treatment with this drug.

In the United States, physicians have to obtain written consent from their patients.

Despite these precautions, cases of pregnancies during treatment with isotretinoin continue to be reported. A French study reviewed 148 pharmacovigilance reports related to isotretinoin intake during pregnancy from January 1, 2003 to December 31, 2006. In 35 cases, conception occurred less than one month after isotretinoin discontinuation, in 89 cases conception occurred during treatment and in 24 cases treatment was initiated in pregnant women. Malformations compatible with fetal retinoid syndrome were described in 4% of the pregnancies (14). In the Netherlands, 51 cases of isotretinoin exposure among 203'962 pregnancies were reported between January 1, 1999 and September 1, 2007. Six fetuses were exposed less than one month after discontinuation of isotretinoin treatment and 45 during pregnancy. In five of the 51 isotretinoin exposed pregnancies (53 exposed fetuses) an adverse fetal or neonatal outcome was observed (15).

Both studies, as well as our own case report, demonstrate that compliance with pregnancy prevention programs remains incomplete with dramatic consequences for some infants and their parents (14, 15). In Switzerland, only verbal information and consent are required (13). In contrast, other countries insist on written consent and strict monitoring during therapy with isotretinoin. Our observation combined with

additional evidence from the literature suggests that the Swiss recommendations may have to be revised.

REFERENCES

1. Browne H, Mason G, Tang T. Retinoids and pregnancy: an update. The Obstetrician & Gynecologist 2014;16:7-11 *(Full text)*

2. Fetal Retinoid Syndrome - NORD (National Organization for Rare Disorders) *(Full text)*

3. Isotretinoin and pregnancy. Medscape [cited 2015 Sep 2] (no abstract available)

4. Azaïs-Braesco V, Pascal G. Vitamin A in pregnancy: requirements and safety limits. Am J Clin Nutr 2000;71:1325s-1333s *(Abstract)*

5. Morrison DG, Elsas FJ, Descartes M. Congenital oculomotor nerve synkinesis associated with fetal retinoid syndrome. J APPOS 2005;9:166-168 *(Abstract)*

6. Van Abel KM, Nelson ME, Collar RM, Lesperance MM. Development of canal cholesteatoma in a patient with prenatal isotretinoin exposure. Int J Pediatr Otorhinolaryngol 2010;74:1082-1084 *(Abstract)*

7. Aguilar S, Louis C, Hicks J, Zage P, Russell H. Congenital neuroblastoma in a neonate with isotretinoin embryopathy. J Pediatr Hemat Oncol 2014;36:e75-e7 *(Abstract)*

8. Troncoso Sen M, Rojas HC, Bravo CE. Isotretinoin embryopathy: report of one case. Rev Med Chil 2008;136:763-766 *(Abstract)*

9. Sarici D, Akin MA, Kurtoglu S, Uzum K, Kiraz A. Asymmetric crying face in a newborn with isotretinoin embryopathy. Pediatr Dermatol 2013;30:e289-e290 *(Abstract)*

10. Pachajoa H, Ordoñez A. Isotretinoin embryopathy with microtia-anotia and congenital heart disease: case report. Arch Argent Pediatr 2012;110:e47-e49 *(no abstract available)*

11. Henrique de Souza Lima G, Raquel Ramos Jubé M, Campelo Feres C, Eizo Watanabe L, Costa de Souza ÂM. Retinoic acid embryopathy: report of two cases associated with the use of isotretinoin. Acta Fisiátrica 2008 Jan 28 (no abstract available)

12. Lee SM, Kim HM, Lee JS, et al. A case of suspected isotretinoin-induced malformation in a baby of a mother who became pregnant one month after discontinuation of the drug. Yonsei Med J 2009;50:445-447 *(Abstract)*

13. Isotrétinoïne par voie orale dans le traitement de l'acné, indication autorisée, précautions et pharmacovigilance. Une mise à jour. Swissmedic 2008 (no abstract available)

14. Autret-Leca PE, Kreft-Jais C, Elefant E, et al. Isotretinoin exposure during pregnancy. Drug Saf 2012;33:659-665 *(Abstract)*

15. Zomerdijk IM, Ruiter R, Houweling LMA, et al. Isotretinoin exposure during pregnancy: a population-based study in The Netherlands. BMJ Open 2014;4:e005602 *(Abstract)*

16. Research C for DE and. Drug safety information for healthcare professionals - information for healthcare professionals: isotretinoin (marketed as Accutane) [cited 2015 Oct 29] (no abstract available)

SUPPORTED BY Vifor Pharma

CONTACT Swiss Society of Neonatology
www.neonet.ch
webmaster@neonet.ch