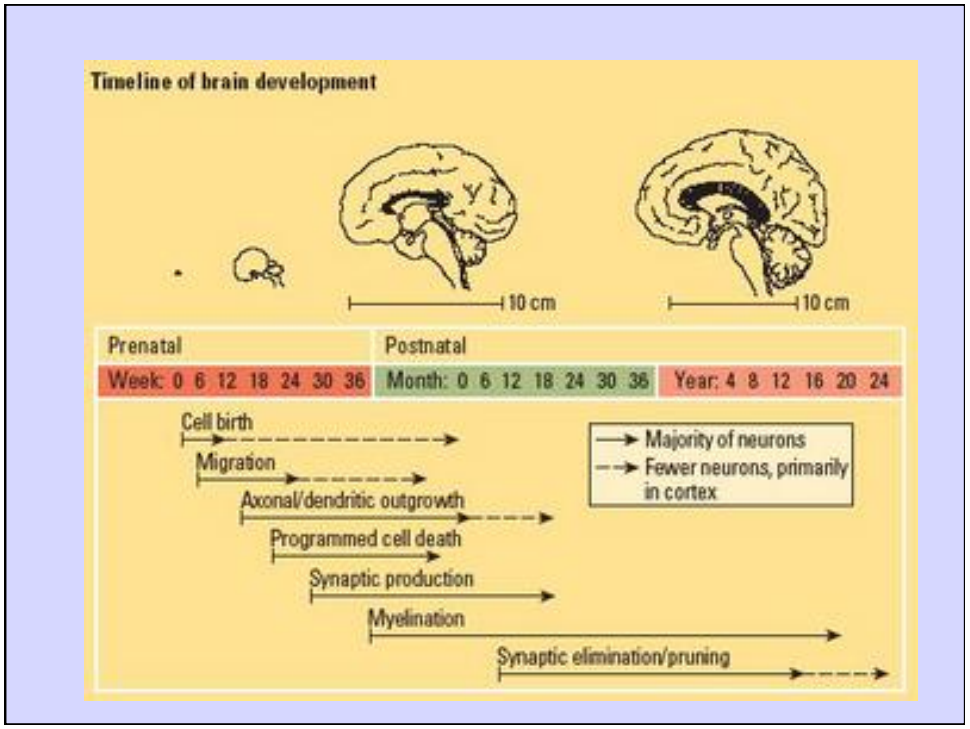
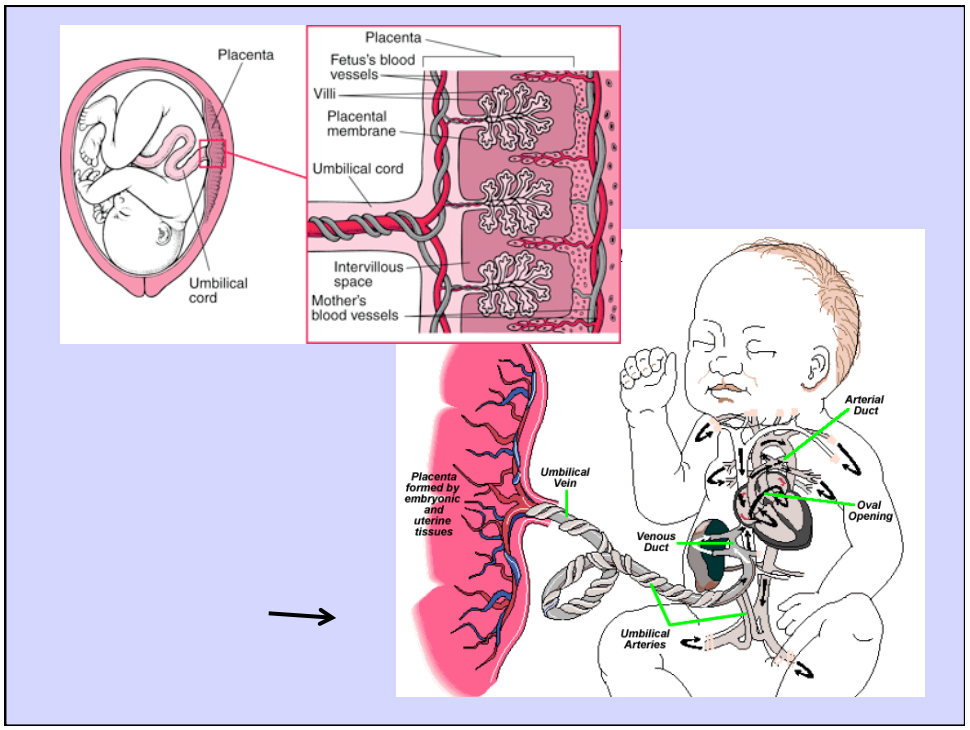
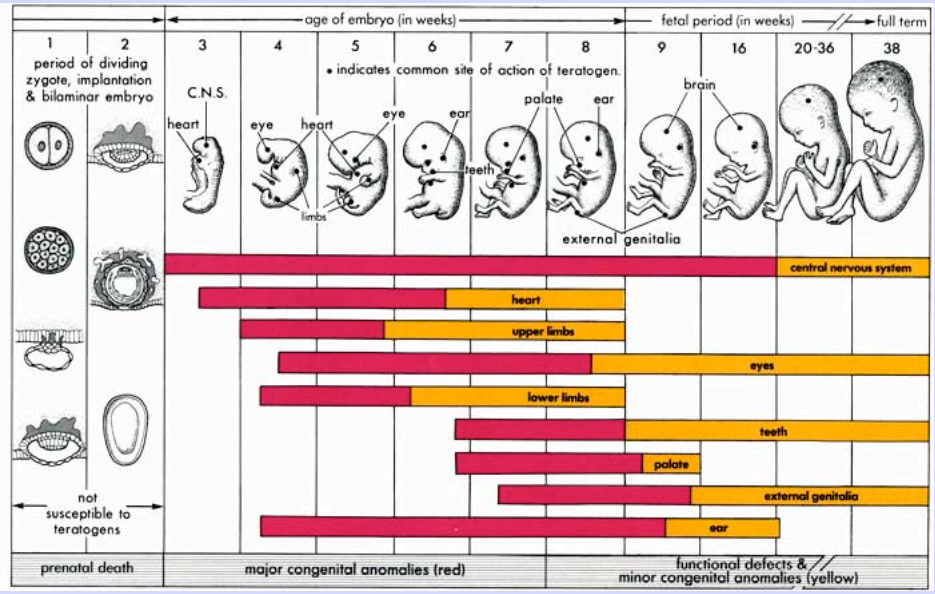

Timeline of brain development
10 cm
10 cm
Prenatal
Postnatal
Week: 0 6 12 18 24 30 36
Month: 0 6 12 18 24 30 36
Year: 4 8 12 16 20 24
Cell birth
Migration
Axonal/dendritic outgrowth
Programmed cell death
Synaptic production
Myelination
Synaptic elimination/pruning
Majority of neurons
Fewer neurons, primarily in cortex

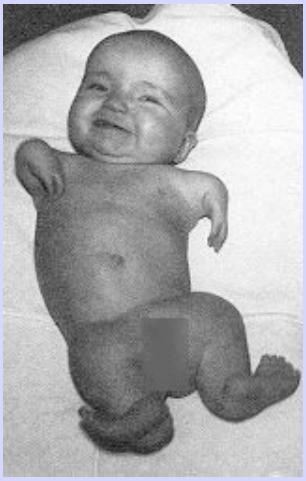

Placenta
Umbilical cord
Placenta
Fetus's blood vessels
Villi
Placental membrane
Umbilical cord
Intervillous space
Mother's blood vessels
Placenta formed by embryonic and uterine tissues
Umbilical Vein
Arterial Duct
Oval Opening
Venous Duct
Umbilical Arteries

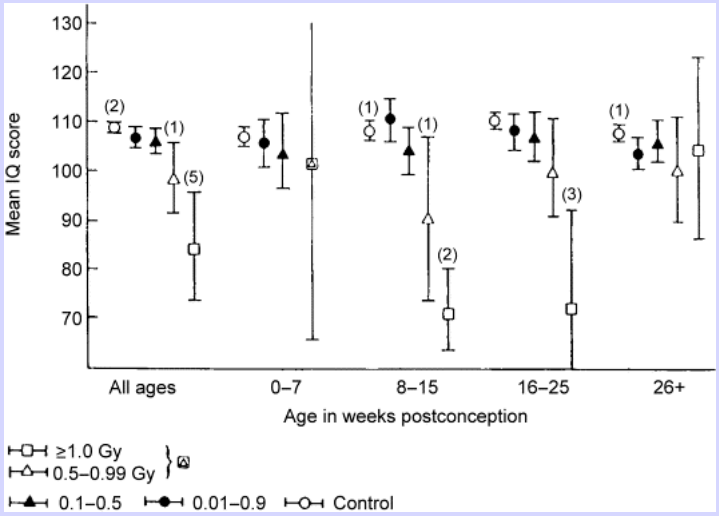
FDA Fetal Risk Factors (a Pregnancy Labeling Task Force has been developed by FDA to label/monitor drugs)

Category	Meaning	?Safe?	Examples
A 1% of meds	-controlled studies show NO risk -adequate, well controlled studies in PG wmn have failed to demonstrate risk to the fetus	Yes	-vitamins -minerals -levothyroxine -maybe insulin
B 19% of meds	-no evidence of risk in humans -either animal findings do not, or if no adequate human studies have been done, animal findings are negative	Yes	-acetaminophen -Insulin -cimetidine -amoxicillin -erythromycin
C 66% of meds	-risk cannot be ruled out -human studies are lacking & animal studies are either positive for fetal risk or lacking as well; however, potential benefits may outweigh risks	Maybe, weigh benefits vs. risks -most drugs are "C" b/c not enough studies are done	-tons
D 7% of meds	-positive evidence of risk -investigational or post-marketing data show risk to the fetus; potential benefits MUST outweigh the risks (i.e. drugs needed for a life-threatening situation or for a serious dis for which safer drugs cannot be used or are infective)	Caution	-phenytoin -narcotic analgesics @ high doses -NSAIDs @ high doses for long period of time
X 7% of meds	-contraindicated in pregnancy -studies in animal or humans, or investigational or post-marketing reports, have shown fetal risk which clearly outweighs any possible benefit to the patient	Avoid!	-thalidamide -accutane -ACE/ARBs -Warfarin -Methotrexate



Thalidomide was used in the 1950'5 to treat morning sickness, largely without testing. Later it was found that fetal exposure to thalidomide between days 35 and 48 was causing severe limb and organ defects in 20-30% of offspring.





Intelligence test scores (IQ) by post-conception age at irradiation and radiation dose in the Japanese atomic bomb cohort.

Article

Atypical Antipsychotic Administration During Late Pregnancy: Placental Passage and Obstetrical Outcomes

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Stephanie Winn, M.D.
Bettina T. Knight, B.S.N., R.N.
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Zachary N. Stowe, M.D.

Objectives: There are limited data regarding the use of atypical antipsychotic medications in pregnancy. The objectives of the current study were to quantify placental permeability to antipsychotic medications and to document obstetrical outcomes for women taking these agents proximate to delivery.

Method: The authors conducted a prospective observational study of women treated with an atypical antipsychotic or haloperidol during pregnancy. Maternal and umbilical cord plasma samples collected at delivery were analyzed for medication concentrations. Placental passage was defined as the ratio of umbilical cord to maternal plasma concentrations (ng/ml). Obstetrical outcome was ascertained through maternal reports and reviews of obstetrical records.

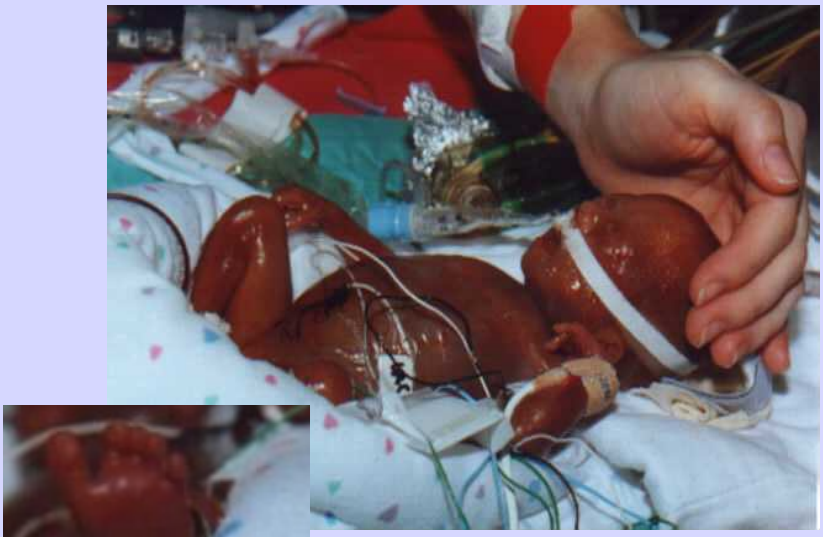
Results: Fifty-four pregnant women with laboratory-confirmed antipsychotic use proximate to delivery were included in the analysis. Complete maternal-infant sample pairs were available for 50 participants. Placental passage ratio was highest for olanzapine (mean=72.1%, SD=42.0%), followed by haloperidol (mean=65.5%, SD=40.3%), risperidone (mean=49.2%, SD=33.9%), and quetiapine (mean=23.8%, SD=11.0%). There were tendencies toward higher rates of low birth weight (30.8%) and neonatal intensive care unit admission (30.8%) among neonates exposed to olanzapine.

Conclusions: All four antipsychotics demonstrated incomplete placental passage. Quetiapine demonstrated the lowest placental passage of the medications studied. These novel data provide an initial quantification of the placental passage of antipsychotics and fetal exposure in humans, demonstrating significant differences between individual medications.

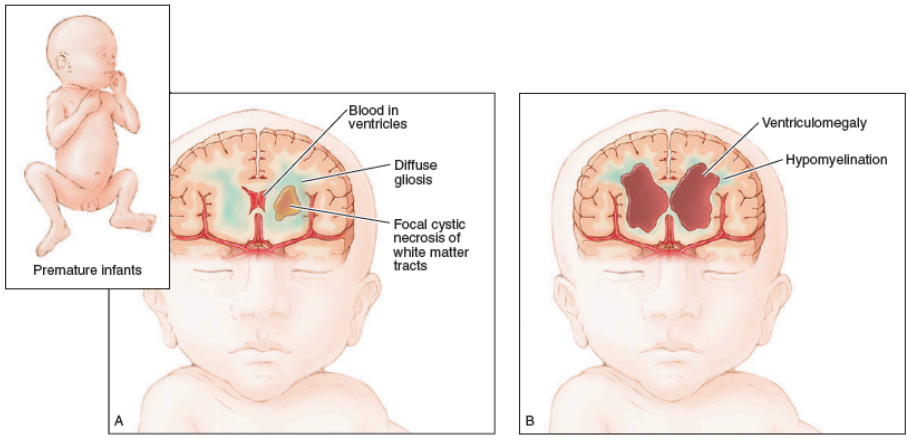
(Am J Psychiatry 2007; 164:1214–1220)

	Risk factor	Reference	Quality of evidence produced by the studies
Prenatal viral infection	Maternal infection, autoimmune disease, and/or allergy could alter the immune status of the fetal brain and the fetal immune system in general	Arndt et al. (2005), Libbey et al. (2005), Miller et al. (2005), Patterson (2009), Pardo et al. (2005), Bilstner (1974), Meyer et al. (2007), Fox et al. (2012), Anderson et al. (2007)	The results have been replicated multiple times and the evidence for an association of altered immune status and ASD is strong and growing
Zinc deficiency	A high incidence rate of zinc deficiency is seen in autistic children. Maternal/early developmental zinc deficiency might provide a mechanism of gene/environment interaction	Lakshmi Priya and Geetha (2011), Faber et al. (2009), Jen and Yan (2010), Walsh et al. (2001, 2002), Yasuda et al. (2011), Golub et al. (1995), Sandstead et al. (1978)	The results have been replicated multiple times, recently using a large cohort of 1,967 autistic children. Based on the data, a strong association of zinc deficiency and autism is found
Abnormal melatonin synthesis	Genetic abnormalities and/or environmental factors may influence melatonin synthesis. Melatonin regulates the circadian rhythm, is an antioxidant, is involved in the immune response, and regulates synaptic plasticity	Rossignol and Frye (2011), Cortesi et al. (2010), Melke et al. (2008), Feng et al. (2012)	Few but high-quality studies report an association of abnormal melatonin synthesis and autism. Genetic studies hint towards a decrease in melatonin as causative rather than aftereffect of autism. However, more research is needed to strengthen the association and propose a patho-mechanism
Maternal diabetes	Obesity and diabetes occur more frequently in mothers of ASD cases. Diabetes in the mother during pregnancy leads to a twofold increased risk	Gardener et al. (2009), Krakowiak et al. (2012)	Meta-analysis confirmed maternal diabetes as risk factor. However, the number of studies is small and others have not found a significant association. It is likely that in some cases of diabetes, downstream effects might act as risk factor for autism. However, more molecular biological research is needed to identify the possible patho-mechanisms
Prenatal and perinatal stress	Autism has been reported to be associated with prenatal stress. In animals, regardless of the specific prenatal stressor used, prenatal stress activated the HPA axis resulting in abnormalities in postnatal immune function	Ward (1990), Beversdorf et al. (2005), Kinney et al. (2008), Limperopoulos et al. (2007)	Stress can refer to factors that range from mechanical to purely psychological ones. The best association of "stress" with autism is seen by factors activating the HPA axis, which might be related to alterations in the immune system. Future research will have to closer investigate specific stressors and the related cellular and molecular alteration
Toxins	The incidence of autism is significantly higher in children prenatally exposed to valproic acid or thalidomide. Organophosphate and organochlorine pesticides may contribute to autism as well as psychiatric drugs taken by the mother during pregnancy	Moore et al. (2000), Stromland et al. (1994), Kolozsi et al. (2009), Kumar and Chhibber (2011), Kumar et al. (2010), Kalr et al. (2007), Dufault et al. (2012), Roberts et al. (2007), Szpir (2006), Gardener et al. (2009)	A limited number of cases and studies makes the findings hard to interpret resulting in a rather weak association of toxins as risk factor and the development of autism. A more solid association can be found in the use of psychiatric drugs in the mother during pregnancy. However, this association might be explained in a number of ways, which need further investigation
Parental age	The risk to develop autism is associated with advanced age in either parent. While most mutations accumulate in the paternal germline, advanced maternal age might contribute through mechanisms such as increased pregnancy complications and maternal autoimmunity	Gardener et al. (2009), Shelton et al. (2010), Parner et al. (2012), Sandin et al. (2012), Kong et al. (2012), van Balkom et al. (2012), Buizen-Voskamp et al. (2011), Grether et al. (2009), Croen et al. (2007), Reichenberg et al. (2010)	Meta-analysis of multiple studies confirmed parental age as risk factor for ASD. The result is underlined by recent genetic studies specifically revealing an increased paternal mutation rate as possible patho-mechanism
Postnatal risk factors	Gastrointestinal or immune system abnormalities, allergies, and exposure of children to drugs, infection, certain foods or heavy metals have been proposed as risk factor for autism	Iebba et al. (2011), Liu et al. (2005), Sahley and Panksepp (1987), Wills et al. (2007), Cohen et al. (1982), Rossi-George et al. (2011), Kinnell (1985), Cohen et al. (1976)	The evidence for the discussed postnatal risk factors needs further substantiation. While it seems plausible that some of the factors can affect brain development prenatally, their postnatal mode of action needs further investigation

Summary statements about each of the environmental factors. The quality of evidence produced by the published studies is weighted based on the replicability and strength of association.



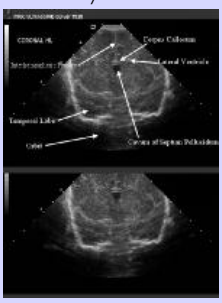
Premature infant at 23 weeks
(term = 40 weeks)



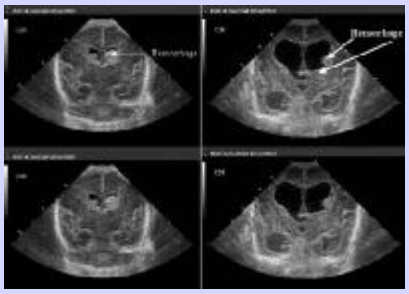
Cerebral palsy and periventricular leukomalacia

Injuries in premature infants include hypoxic (reduced oxygen) and ischemic (reduced bloodflow) events (HI injuries), such as Periventricular-Intraventricular Hemorrhage (PVH-IVH or "intra-cranial bleed")

Bleed in the subependymal germinal matrix, fragile capillary network in developing brain. Consequences include destruction of cerebral parenchyma, posthemorrhagic hydrocephalus. Classified in 4 grades of severity.



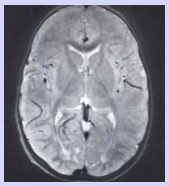
Sonographic appearance of a normal neonatal brain (coronal midline scan).
From eMedicine.



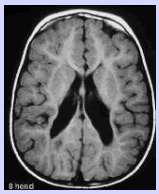
Severe Grade III hemorrhage (sub-ependymal with significant ventricular enlargement; coronal midline scan).
From eMedicine.

Periventricular Leukomalacia (PVL):

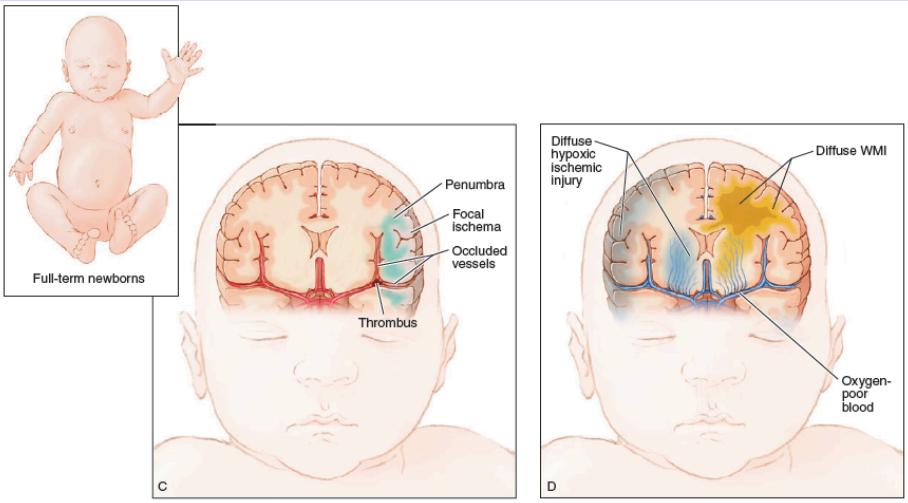
Disorder of periventricular white matter. Occurs by nonhemorrhagic ischemic necrosis. Consequences include loss of white matter around lateral ventricles.



Cranial MRI, healthy **16-month-old.**



Cranial MRI (T1-weighted, axial), **18-month-old** with PVL. The lateral ventricles are enlarged without hydrocephalus. The periventricular white matter is diminished.
C/B Matthew Omojola, MD



Neonatal stroke

Hypoxic ischemic encephalopathy

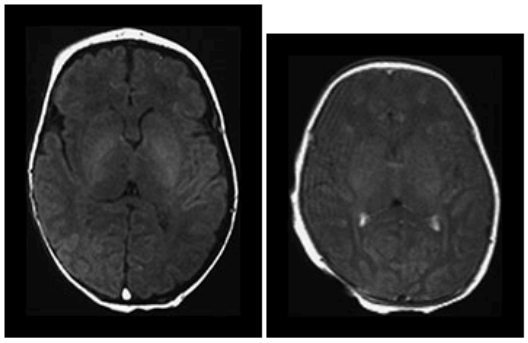
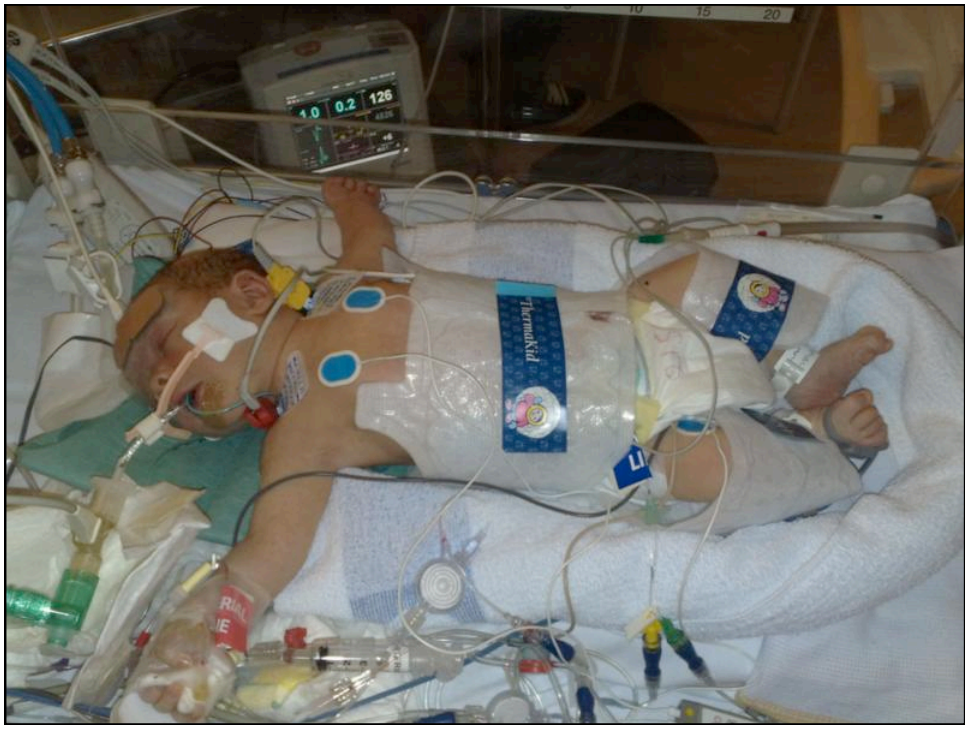


Fig. 6.1 Brain swelling. T1 weighted spin echo sequence (SE 860/20) of two different term-born infants aged 2 days. (a) Normal brain with no obvious swelling. The ventricles of a normal term-born infant are usually narrow. (b) Severe brain swelling showing slit-like ventricles, complete 'closure' of the interhemispheric fissure and no visible extracerebral space or sulci.



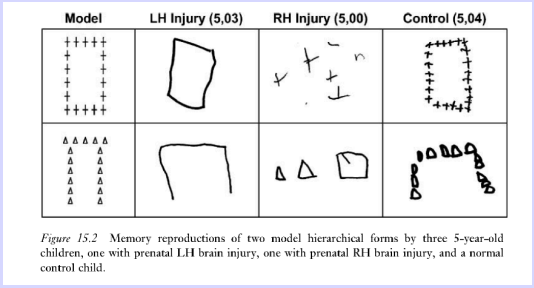


Figure 15.2 Memory reproductions of two model hierarchical forms by three 5-year-old children, one with prenatal LH brain injury, one with prenatal RH brain injury, and a normal control child.

- Children with early focal brain damage ultimately reach levels of performance well ahead of those observed in adults with homologous injuries.
- [Stiles et al.] results for spatial cognition are... similar to .. lesion-symptom patterns ...for brain-injured adults. In the spatial domain, RHD [is] associated with a deficit in the integration of information; .. LHD results in a deficit in the extraction of pattern detail. Child findings for language development are *not at all* compatible with the classic aphasia types observed in adults. Deficits in word comprehension and gesture appear to be associated with RHD rather than LHD (although deficits on the production of words and grammar are greater in LHD sample). It is possible that language is more plastic than other behavioral functions simply because it is a phylogenetically recent phenomenon.....Stiles et al. suggest "... language is a parasitic system, running on hardware that evolved for other purposes."
- Children with focal brain injury (R or L) eventually surpass ... other clinical groups [such as SLI, ASD, Williams, ID, Downs], even though recent neural imaging studies of SLI, autism, Williams Syndrome and Down Syndrome provide no evidence for frank lesions of any kind.