Risks of aluminium exposure during pregnancy

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Abstract

It is well known that aluminium is potentially neurotoxic. Moreover, there has been concern in recent years that dietary and environmental exposure to aluminium might cause developmental toxicity in mammals. While it is well established that aluminium may be a developmental toxic when administered parenterally, until recently there was little concern about embryo/fetal consequences of aluminium ingestion because bioavailability was considered low. This paper summarizes the results of recent investigations on the embryo/fetal toxicity of aluminium, the potential reproductive toxicology of aluminium, and the neurodevelopmental and behavioural effects deriving from aluminium exposure during pregnancy. Potential therapies to protect against aluminium-induced developmental toxicity are also reviewed.

Key words: Aluminium, pregnancy, embryo/fetal toxicity, neurodevelopmental and behavioural effects, chelating agents.

Resum

És ben conegut que l'alumini és potencialment neurotòxic. En els darrers anys s'ha plantejat si l'exposició dietètica i mediambiental a l'alumini podia causar toxicitat en el desenvolupament dels mamífers. Mentre que està ben establert que l'alumini pot ser un tòxic per al desenvolupament quan s'administra parenteralment, fins fa poc no hi havia gaire inquietud per les conseqüències embrio/fetals derivades de la ingesta d'alumini, ja que la seva biodisponibilitat era considerada baixa. Aquest article resumeix els resultats obtinguts en investigacions recents sobre la toxicitat embrio/fetal de l'alumini, la potencial toxicologia reproductiva d'aquest element, així com els efectes sobre el neurodesenvolupament i el comportament derivats de l'exposició a l'alumini durant la gestació. Finalment, també es revisen les teràpies potencials per protegir-se de la toxicitat causada per l'alumini en el desenvolupament.

Although it is well established that regardless of the host, the route of administration, or the speciation, aluminium (Al) is a potent neurotoxicant [52,72-74,85], the basis for its toxicity is still unkown. Aluminium has been found to be a major causative factor in the development of dialysis encephalopathy [5]. High concentrations of Al are reported in plasma and tissue samples of dialyzed and nondialyzed patients with chronic renal failure [3,5,55]. The toxicity of Al also includes osteomalacia and anemia [34]. In recent years, numerous investigations have also demonstrated that Al disrupts a wide variety of neurological processes.

Moreover, Al has been proposed as a contributor to the pathogenesis of serious neurological disorders such as Alzheimer's disease (AD), amyotrophic lateral sclerosis and parkinsonism-dementia of Guam [59,66,77]. The pathologic features that these neurodegenerative diseases share include abnormal phosphorylation of neuronal cytoskeletal proteins and the abnormal deposition of these proteins in neurons. In susceptible species, Al induces cytoskeletal changes in which neurofilaments accumulate in neuronal cell bodies and proximal axonal enlargement [63,76]. Although Al has been reported to impact on gene expression, this does not appear to be critical to the induction of cytoskeletal pathology [74].

In any case, while there is unequivocal evidence that Al is a potent neurotoxic agent inducing neurofibrillary degeneration in animal brains after intracerebral Al injections and systemic Al exposure [72-75], the association between Al exposure and the pathogenesis of AD and related disorders remains unproven and questionable [23,33,50,70]. However, a number of reports in the recent literature strongly sug-

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gest that, by limiting human exposure to unnecessarily high Al concentrations, the incidence of AD might be reduced [53,58,60].

With respect to potential Al toxicity, until recently, there was relatively little concern about toxic consequences of Al ingestion because it was assumed that Al was not orally bioavailable. However, in recent years, it has been shown that although the gastrointestinal tract normally represents a major barrier to Al absorption, under some circumstances this barrier can be breached [3,4]. Consequently, individuals ingesting large amounts of Al compounds do absorb a definite amount of Al [3]. Aluminium absorption, excretion, tissue retention, and deposition all depend on the properties of the Al^{3+} complexes formed with biological ligands. The complexity in the aqueous chemistry of Al has also affected Al toxicity studies [54].

Normally, mammals maintain very low Al concentrations in their tissues because of a combination of low intestinal uptake and rapid clearance. However, it is now recognized that toxicity can occur either if absorption is markedly increased or renal clearance is impaired. Although most foods contain small but variable amounts of Al, the exposure to Al through the diet is small compared to the quantities of Al in many antacid products, some buffered analgesics and other therapeutic preparations [24]. Some people consume as much as an additional 5 g of Al daily from these compounds [51,56].

Aluminium-containing antacids are widely used nonprescription medications, which have been administered for many years for the treatment of various gastrointestinal disorders. During pregnancy, dyspepsia is a common complaint and antacids are widely used to reduce the dyspeptic symptoms. In most of these drugs, Al is present as Al hydroxide, which has a very low aqueous solubility. However, the consumption of high amounts of Al compounds during pregnancy can mean a potential risk of Al accumulation because of the relatively great number of dietary constituents (ascorbate, citrate, lactate, succinate, etc.), which can enhance the gastrointestinal Al absorption [28,29,31].

Until recently, information on human studies to determine whether Al ingestion could have adverse effects on the outcome of pregnancies was very scarce. In 1986, Weberg et al. [78] reported that since it was not clear whether maternal Al could increase the Al levels in the fetus, high-dose antacids should not be consumed during pregnancy. More recently, Golding et al. [36] carried out studies to determine whether Al sulfate accidentally added to a local water supply (Cornwall, United Kingdom) had adverse embyo/fetal effects in pregnant women. It was concluded that although a lack of major problems associated with fetal exposure to high Al doses was noted, the relatively small number of pregnancies made it impossible to say that high doses of Al sulfate would be safe during gestation. On the other hand, the literature contains little information regarding either the experimental embryotoxic and teratogenic potential of Al, or the effects of gestational exposure to Al on the fetus and newborn. In order to obtain an overall understanding of the reproductive and developmental toxicity of Al, an extensive research program on these topics was initiated in our laboratory in the mid-1980s. Data about Al-induced embryo/fetal toxicity, the potential reproductive toxicology and the postnatal effects of Al are here reviewed with special attention to our results.

Embryo/fetal toxicity of aluminium

It is now well established that Al may be an embryo/fetal toxin depending on the route of exposure and/or the solubility of the Al compound administered. While Al chloride was found to be embryotoxic and teratogenic when given parenterally to rats and mice [8,18,20,79], no evidence of maternal and embryo/fetal toxicity was observed when high doses of Al hydroxide were given to pregnant rats and mice. Thus, no developmental effects of Al hydroxide were observed when Al hydroxide was given orally to rats at 66.5, 133, and 266 mg Al/kg/day [44] or mice at 23, 46, and 92 mg Al/kg/day [27] during organogenesis. In addition, the maternal-placental Al concentrations were not significantly different between control and Al-treated rats, while Al could not be detected in the whole fetuses in any of the groups [44]. These results indicate that Al from Al hydroxide is very poorly absorbed and does not reach the fetus at levels, which might mean a developmental hazard. In mice, for example, the doses of Al hydroxide would be equivalent to those consumed by people of 60 kg body weight who ingest 1.4, 2.8 or 5.5 g of Al per day, respectively, which are much higher than the amounts usually ingested for peptic disorders.

In contrast to this, in a previous study oral administration of Al nitrate nonahydrate (13, 26 and 62 mg Al/kg/day) to pregnant rats on gestation days 6-14 resulted in decreased fetal body weight and increased the incidence and types of external, visceral, and skeletal malformations and variations in all the Al-treated groups [65]. It was concluded that although embryolethality was not induced in rats by oral Al administration, teratogenic effects might result at Al nitrate doses as high as those administered in that study, corresponding approximately to 1/20, 1/10, and 1/5 of the acute oral LD_{50} of Al nitrate nonahydrate for adult female rats [57]. These data together with those obtained from studies in which Al hydroxide was given orally to rats and mice [27,44] show that Al compound solubility plays an essential role in the potential embryo/fetal toxicity of Al.

In recent years, it has been demonstrated that ingestion of Al hydroxide concurrently with fruit juices or with some common organic constituents of the diet (citrate, ascorbate, lactate, succinate, etc.) causes a marked increase in the gastrointestinal absorption of Al in healthy individuals [28-31,69]. The presence of Al complexing compounds in the gastrointestinal tract with gastric acid solubilizes Al cations and may thus result in the equilibrium formation of a soluble complex of Al, which by preventing reprecipitation, may result in Al absoprtion [64]. Taking this into account, we investigated whether the concurrent ingestion of citric, lactic or

Table 1. Maternal and embryofetal toxicity of aluminium compounds: A summary of various studies[1]

Aluminium Compound	Dose mg Al/kg/day	Species	Route	Maternal Toxicity	Embryo/Fetal Toxicity	Reference
Al hydroxide	23, 46, 92	Mice	PO	No adverse effects	No adverse effects	27
Al hydroxide	66, 132, 266	Rats	PO	No adverse effects	No adverse effects	44
Al chloride	15, 20, 40	Rats	IP	Maternal deaths (at 40 mg Al/kg/day). Reduced body weight gain	Embryolethality, growth retardation, fetal abnormalities, (at 20 and 40 mg Al/kg/day)	8
Al chloride	20, 30, 40	Mice	IP	No adverse effects	Decreased fetal weight, increased number of resorptions	20
Al lactate	10, 20, 40	Mice	SC	No adverse effects	Decreased fetal crown-rump lengths (at 20 mg Al/kg/day)	39
Al nitrate nonahydrate	13, 26, 52	Rats	PO	Reduced body weight gain and food consumption	Fetotoxicity including teratogenic effects	65
Al hydroxide + citric acid (62 mg/kg/day)	133	Mice	PO	Reduced body weight gain	Reduced fetal body weight, increase in the incidence of skeletal variations	45
Al hydroxide + lactic acid (570 mg/kg/day)	57	Mice	PO	Reduced body weight gain	Reduced fetal body weight, increase in the incidence of skeletal variations	16
Al hydroxide + ascorbic acid (85 mg/kg/day)	104	Mice	PO	No adverse effects	No adverse effects	17

[1] Data from Domingo [21]

ascorbic acid and high doses of Al hydroxide might result in developmental toxicity in mammals.

The concurrent oral administration of citric acid (62 mg/kg/day) and Al hydroxide (133 mg Al/kg/day) to rats on gestation days 6-15 did not modify the lack of embryotoxicity and teratogenicity previously reported. However, the incidence of skeletal variations (delayed ossification of occipital and sternebrae) was significantly increased [45]. Although not significantly different, the incidence of skeletal variations also increased in fetuses of pregnant mice given oral doses of Al hydroxide (57 mg Al/kg/day) and lactic acid (570 mg/kg/day) on days 6-15 of gestation, in comparison with a group of animals receiving Al hydroxide (57 mg Al/kg/day) only [16]. By contrast, no signs of developmental toxicity were observed in mice when Al hydroxide (104 mg Al/kg/day) was given by gavage concurrently with high doses of ascorbic acid (85 mg Al/kg/day) on gestation days 6-15 [17].

A summary of the above studies is presented in Table 1.

Effects of aluminium on postnatal development and behaviour of the offspring

The effects on reproduction, gestation, parturition and lactation of oral Al exposure (0, 13, 26 and 52 mg Al/kg/day given as Al nitrate nonahydrate) were assessed in rats [25,26]. Male rats were treated orally for 60 days prior to mating with mature virgin female rats treated for 14 days prior to mating with treatment continuing throughout mating, gestation, parturition, and weaning of the pups. One-half of the dams in each group were killed on gestation day 13 and the remain-

ing dams were allowed to deliver and wean their offspring. Although no adverse effects on fertility or general reproductive parameters were noted, the survival ratios were higher in the control group. A dose-dependent delay in the growth of the living pups was also observed in all Al-treated groups [25]. The growth of the offspring was also significantly delayed when in a subsequent experiment Al nitrate nonahydrate (52 mg Al/kg/day) was given orally to rats from birth throughout lactation [26].

Yokel [80-82] reported few effects in the suckling offspring of rabbits whose does received subcutaneous injections of Al lactate at doses of 0.68, 2.7 or 10.8 mg Al/kg/injection, which was attributed to a probable limited distribution of Al into milk, together with a poor gastrointestinal Al absorption [80,83]. These studies, as well as other investigations conducted on rats and mice, indicated that Al is present in the milk of Al-exposed dams but that it would not readily accumulate in pups during lactation [37]. By contrast, although in the placenta of pregnant rabbits and mice, Al concentrations were found to be four- to five-fold higher than those found in most fetal or maternal soft tissues of rabbits and mice, accumulation in the placenta did not apparently lessen or prevent Al accumulation in the fetus [37,38]. This could indicate that the delay on postnatal development following Al exposure is due to an Al accumulation in the fetuses, rather than Al absorption from the milk of the dam. However, a lack of remarkable Al transfer with lactation would not necessarily indicate that elevated Al in milk does not cause adverse effects on the offspring. Golub and co-workers [43] showed that nursing pups of mouse dams fed excess Al in their diet exhibit poor retention of iron and manganese from a milk meal. However, subcuta-

Table 2. Neurodevelopmental toxicity of aluminium compounds: A summary of various studies[1]

Aluminium Compound	Dose	Species	Route	Neurodevelopmental Effects	Reference
Al lactate	500, 1000 ppm	Mice	Diet	Hindlimb paralysis, seizures and death. Altered performance on a neurobehavioural test battery (foot splay, forelimb and hindlimb grip strengths, thermal sensitivity)	39
Al lactate	0.5 and 1 mg Al/g diet	Mice	Diet	Reduced motor activity	40
Al lactate	1 mg Al/g diet	Mice	Diet	Reduced forelimb grasp strength, impaired negative geotaxis, decreased temperature sensitivity	41
Al lactate	1 mg Al/g diet	Mice	Diet	Decreased motor activity, decreased grip strength, decreased startle responsiveness	41
Al lactate or Al chloride	100-400 mg Al/kg/day	Rats	PO	Delay in neuromotor maturation of pups, (righting reflex, grasping reflex, negative geotaxis, locomotor coordination), increase in postnatal death rate, growth retardation	9,10,62

[1] Data from Domingo [21]

neous administration of Al lactate (2.5-10 mg/kg/day) to rats on gestational days 7-15 had no effect on birthweight, mean litter size, and the day of eye and ear opening [48]. Similar findings were also reported by Muller et al. [62] and Yokel [81].

On the other hand, a number of studies conducted in rats and mice show that maternal oral Al exposure can alter performance on a neurobehavioural test battery, specifically impaired negative geotaxis, and reduced forelimb and hindlimb grip strength [9,10,32,39-42]. A markedly reduced activity level during behavioural testing was reported in adult rats after developmental Al exposure [15,62]. However, no deficits in the test of delayed alterations [43], in the radial maze [15], or in the operant light avoidance task [62] were found in adult mice and rats exposed to Al during development. Notwithstanding, Gonda et al. [49] reported that although the learning ability of the pups of rats given 9.8 mg/kg/day of Al lactate on gestation days 7-15 was impaired in a passive avoidance task, no effect on the acquisition of a conditioned taste aversion was noted. In turn, Poulos et al. [67] showed that oral Al administration to rats during pregnancy and lactation produced delay in the development of the central nervous system of their pups. The relevance of these findings for children exposed to Al still needs to be determined by extending the evaluations to more complex CNS functions, including learning, regulation of arousal and sensory abilities [37]. The most striking results of a number of these studies are summarized in Table 2.

Developmental effects of aluminium and stress

A number of studies in mammals have shown that during pregnancy, maternal stress from restraint, noise, light, and heat among others may be associated with adverse effects on embryo/fetal development [68]. Of special concern is the finding that interaction between maternal stress and some

chemical teratogens can enhance the developmental toxicity of those chemicals.

Since Al is ubiquitous, exposure to this element is in fact unavoidable. This means that pregnant women may be potentially exposed to Al in food, drinking water, soil ingestion, and some medications. They may also be concurrently exposed to various types of stress, either at home or in the workplace. Because both Al and maternal stress during pregnancy have been shown to produce adverse developmental effects in mammals, we investigated the developmental toxicity in mice of a combined exposure to Al and maternal stress [18,19]. The model stressor used was maternal immobilization. Among the animal models to examine the effects of maternal stress on the embryo/fetal toxicity of a chemical, restraint has been widely used.

In a first study, the potential interaction between Al and maternal restraint stress was assessed in mice. Four groups of plug-positive female mice were given intraperitoneal injections of $AlCl_3$ at 37.5 and 75 mg/kg/day on days 6-15 of gestation. Two of these groups were also subjected to restraint for 2 h/day during the same gestational days. Maternal toxicity was significantly enhanced by restraint stress at 75 mg $AlCl_3$/kg/day. No signs of embryo/fetal toxicity were observed following exposure to Al, maternal restraint, or combined Al and restraint. However, a significant decrease in fetal body weight, as well as a significant increase in the number of litters with morphologic defects was observed in the group exposed to 75 mg $AlCl_3$/kg/day plus maternal restraint (Table 3). These results suggest that maternal stress exacerbates Al-induced maternal and developmental toxicity only at high Al doses of the metal, which are also toxic to the dam [18].

In a subsequent investigation, we assessed the potential influence of maternal restraint stress and Al on the postnatal development and behaviour of the offspring. On days 6-15 of gestation, two groups of pregnant mice received intraperitoneal injections of $AlCl_3$ at 75 mg/kg/day. One of

Table 3. Effects of restraint stress on developmental toxicity of aluminium in mice[1]

	Control group	Restraint alone	AlCl$_3$ alone (37.5 mg/kg)	AlCl$_3$ (37.5 mg/kg) + restraint	AlCl$_3$ alone (75 mg/kg)	AlCl$_3$ (75 mg/kg) + restraint
No. of Plug-Positive Females (day 0)	12	9	11	14	14	17
Deaths	0	0	1	2	2	2
Abortions	0	0	0	4	2	7
Early Deliveries	0	0	0	0	0	0
Evaluated at Term	12	9	10	8	10	8
Resorbed Litters	0	0	0	0	0	0
No. of Litters	12	9	10	8	10	8
Body Weight at Termination (g)	54.26±5.69	51.02±3.64	51.94±1.90	49.76±4.82	51.47±2.52	51.53±3.71
Gravid Uterine Weight (g)	18.51±3.93[a]	18.77±3.20[a]	16.44±0.92[ab]	14.59±3.68[b]	14.65±2.76[b]	14.85±2.60[b]
Corrected Body Weight (g)	36.08±5.43[ab]	32.24±0.92[b]	35.18±1.19[ab]	36.23±5.77[ab]	37.03±2.62[a]	36.43±2.21[a]
Corrected Body Weight Change (g)	9.26±2.24[ab]	7.57±9.54[b]	9.44±2.14[ab]	10.52±4.40[a]	11.27±1.74[a]	7.44±2.09[b]
Fetal Body Weight (g)	1.30±0.11[a]	1.26±0.12[ab]	1.13±0.08[bc]	1.05±0.16c[d]	1.06±0.11[cd]	0.91±0.15d
Total Fetuses with Internal or Skeletal Defects (Litters)	5 (4)[a]	7 (3)[a]	5 (3)[a]	3 (3)[a]	5 (3)[a]	31 (8)[b]

[1]Data from Colomina et al. [18]. Results are presented as means ± SD. Values in the same row not showing a common superscript (a,b,c,d) are significantly different (p < 0.05).

these groups was also subjected to restraint for 2 h/day during the same days of gestation. The pups were evaluated for physical development, neuromotor maturation and behaviour on postnatal days 22, 30 and 60. The results showed that, although no significant effects of maternal Al plus restraint on the behaviour of the offspring were noted, a significant influence of maternal stress on Al-induced postnatal developmental effects was observed [19]. This agrees with the previous results showing that maternal stress could enhance the Al-induced embryo/fetal toxicity in mice [18].

Protective effects of chelators on Al-induced maternal and developmental toxicity

Chelating agents such as desferrioxamine (DFO) and some 3-hydroxypyridin-4-ones can be effective in reducing Al body burdens [46,47,84]. As there were no data on potential chelation therapies to protect pregnant women, infants and children against Al-induced maternal and/or developmental toxicity, recently the protective activity of DFO and deferiprone (1,2-dimethyl-3-hydroxypyrid-4-one, L1), two efficient chelators for the treatment of Al overload, on Al-induced maternal and developmental toxic effects was evaluated in mice.

In a first study, Al chloride was intraperitoneally injected to pregnant mice at 0, 60, 120 and 240 mg/kg/day on gestation days 6-15, while DFO was administered subcutaneously at 40 mg/kg/day on days 6-18 of gestation. In a previous study [14], we found that the non-observable adverse-effect level (NOAEL) for developmental toxicity of parenteral DFO in mice was 176 mg/kg/day. Significant amelioration by DFO of Al-induced maternal toxicity was only noted at 120 mg/kg/day, while no effects were observed of DFO on fetal body weight, the only embryo/fetal parameter significantly

affected by maternal Al exposure [1]. The unexpected lack of Al-induced embryotoxicity found in this study could be due to the chelating activity of DFO on Al^{3+} in dam tissues, which would prevent this ion from reaching the embryo.

In a second study, a single oral dose of Al nitrate nonahydrate (1327 mg/kg) was given to mice on gestation day 12, the most sensitive time for Al-induced maternal and developmental toxic effects in this species. At 2, 24, 48 and 72 hr thereafter, deferiprone was given by gavage at 0 and 24 mg/kg. Aluminium-induced maternal toxicity was evidenced by significant reductions in body weight gain and food consumption, while developmental toxicity was evidenced by a significant decrease in fetal weight per litter and an increase in the total number of fetuses and litters showing bone retardation. No beneficial effects of deferiprone on these adverse effects could be observed. In contrast, a more pronounced decrease in maternal weight gain, as well as an increase in the number of litters with fetuses showing skeletal variations were observed in the group given Al and deferiprone [2].

As both DFO and deferiprone failed to protect against Al-induced maternal and developmental toxicity, we also investigated whether dietary Si could prevent the toxic effects caused by Al in the pregnant animals. The rationale of this study was based on clear evidence showing that oral silicon can reduce the gastrointestinal absorption of Al and increases its elimination [6,84]. The preventive mechanism appears to involve the formation of hydroxyaluminosilicates by the adsorption of silicic acid onto an Al hydroxide template [54]. On gestation days 6-15, Al nitrate nonahydrate (398 mg/kg/day) was given by gavage to three groups of pregnant mice, which also received silicon in drinking water at concentrations of 0, 118 and 236 mg/l on days 7-18 of gestation. Although silicon administration at 236 mg/l significantly reduced the percentage of Al-induced maternal deaths, abortions and early deliveries, neither 118 nor 236 mg/l of silicon produced significant ameliorations on Al-induced fetotoxicity [7].

Conclusions

Al is a well-known developmental toxicant following parenteral exposure [21,22,37]. Moreover, although no evidence of embryo/fetal toxicity was observed when high doses of Al hydroxide were given orally to pregnant rats and mice, some signs of maternal toxicity and fetotoxicity were found when Al hydroxide was given to mice concurrently with citric or lactic acids, or when Al was administered orally as Al nitrate, lactate, or chloride to rats and mice. Theterfore, it seems well established that oral Al exposure during pregnancy can cause a syndrome including growth retardation, delayed ossification, and malformation at Al doses that also lead to reduced maternal weight gain. The severity of these effects is highly dependent on the chemical form of Al administered. In turn, in the postnatal period, reduced pup weight gain and effects on neuromotor development and behaviour can occur as a consequence of maternal and developmental Al exposure.

A recent review by Borak and Wise [13] attempts to minimize the potential toxicity of Al during pregnancy by stating that environmental and dietary Al exposures are unlikely to pose risks of Al accumulation to pregnant animals or their fetuses, but the weight of evidence would seem not to support this statement [38]. In relation to this, the current review shows a lot of evidence on Al-induced maternal and developmental toxicity in rats and mice.

On the other hand, recent attention has also focused on Al toxicity in infants. Moreno et al. [61] reported that both, preterm and full-term neonates are susceptible to Al accumulation in tissues while receiving parenteral nutrition. In turn, Bishop et al. [12] showed that, in preterm infants, prolonged intravenous feeding with solutions containing Al is associated with impaired neurologic development. Bishop et al. [11] had previously shown increased concentrations of Al in the brain of a parenterally fed premature infant.

According to the results of the studies here reviewed, including those on the enhancement of Al absorption from the gastrointestinal tract by certain dietary constituents, the potential effects of maternal stress on Al-induced maternal and developmental toxic effects and the lack of an adequate, safe and effective treatment to protect against these potential adverse effects, indicate the advisablility of avoiding high-dose consumption of Al-containing compounds during gestation and lactation. Data on human studies also suggest this recommendation. The results of Weberg et al. [78], who performed a small trial to assess whether antacids containing Al were safe during pregnancy, and the findings of Gilbert-Barness et al. [35], based on data related to the death of a 9-year-old girl, who failed to progress developmentally at age 2 months, and whose mother ingested very high amounts of Al hydroxide daily during the entire pregnancy, support the hypothesis that Al exposure during pregnancy can be a developmental hazard.

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