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The use of iodinated and gadolinium contrast media during pregnancy and lactation

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Abstract The use of iodinated or gadolinium-based contrast media in pregnant or lactating women often causes concerns in the radiology department because of the principle of not exposing a fetus or neonate to any drugs. Because of the uncertainty about the use of contrast media during pregnancy and lactation, the Contrast Media Safety Committee of the European Society of Urogenital Radiology decided to review the literature and draw up guidelines. An extensive literature search was carried out and summarized in a report. Based on the limited information available, simple guidelines have been drawn up. The report and guidelines were discussed at the 11th European Symposium on Urogenital Radiology in Santiago de Compostela, Spain. Mutagenic and teratogenic effects have not been described after administration of gadolinium or iodinated contrast media. Free iodide in radiographic contrast medium given to the mother has the potential to depress fetal/neonatal thyroid function. Neonatal thyroid function should be checked during the 1st week if iodinated contrast media have been given during pregnancy. No effect on the fetus has been seen after gadolinium contrast media. Only tiny amounts of iodinated or gadolinium-based contrast medium given to a lactating mother reach the milk, and only a minute proportion entering the baby's gut is absorbed. The very small potential risk associated with absorption of contrast medium may be

considered insufficient to warrant stopping breast-feeding for 24 h following either iodinated or gadolinium contrast agents.

Keywords Gadolinium contrast media · Iodinated contrast media · Lactation · Pregnancy

Introduction

When radiological investigations using iodinated contrast media are considered during pregnancy, the principal anxiety for the safety of the fetus relates to exposure to ionizing radiation [1]. However, the potential for harmful effects related to the iodinated contrast agent should also be considered. In early pregnancy, anxiety usually relates to the potential mutagenic and teratogenic effects, while in later pregnancy the possible harmful effect on the fetal thyroid has given cause for concern [2]. When gadolinium-enhanced magnetic resonance scans are undertaken during pregnancy the risk of ionizing radiation is avoided, but again the possible harmful effects of the contrast medium have to be considered.

When imaging involving iodinated and gadolinium agents is undertaken during lactation, the instructions provided by the manufacturers indicate that the baby should not be breast-fed for the 24–48 h after contrast medium is given. However, the available data suggest that only tiny amounts of either type of contrast medium reach the milk, and only a minute amount of contrast medium ingested is then absorbed from the gut. It has been suggested that the manufacturers' recommendation for gadolinium is unnecessarily draconian [3], and in many departments it is current practice for breast-feeding to continue normally after either iodinated or gadolinium contrast agents are given.

Because of the uncertainty about the use of contrast media during pregnancy and lactation, the Contrast Media Safety Committee of the European Society of Urogenital Radiology decided to review the literature and draw up guidelines.

Mutagenicity and teratogenicity of contrast media

No mutagenic effects were shown *in vitro* with three ionic iodinated agents using both bacterial (Ames) testing and sister chromatid exchange methods [4]. *In vivo* tests in animals have shown no evidence of either mutagenic or teratogenic effects with the nonionic iodinated agents [5–12].

There was anxiety about the cytogenic properties of iodinated contrast media when abnormal micronuclei, a measure of chromosomal damage, were detected in lymphocytes following X-ray investigations using contrast media [13, 14]. This effect appears to be similar for both ionic and nonionic agents [15]. A meta-analysis of the effect, which reviewed ten studies, suggested that contrast media enhance the X-ray dose absorbed by lymphocytes suspended in the contrast medium and that this only affected cells circulating in the blood at the time of the examination [16]. It has been suggested that this is a cytotoxic rather than a genetic effect [4].

There is no evidence that gadolinium agents cause chromosomal damage or teratogenic effects. In rats, neither expo-

sure to gadopentetate dimeglumine plus magnetic resonance nor exposure to gadopentetate dimeglumine alone caused anaphase bridge formation, an indicator of chromosome damage [17]. Neither intraperitoneal gadopentetate dimeglumine plus magnetic resonance nor intraperitoneal gadopentetate dimeglumine alone had any detectable effect on the development of mice [18]. No teratogenic effects or effects on postnatal development were seen following gadopentate dimeglumine, gadoteridol, gadobenate dimeglumine, or gadoversetamide use in animals [18–21].

Placental transfer of contrast media

In the human placenta, maternal blood directly surrounds the placental villi and is separated from fetal connective tissue by a layer of chorionic epithelium only [22]. Drugs in maternal blood cross the placenta mainly by simple diffusion, and the chorionic epithelium behaves like other lipid membranes in the body. Thus lipid-soluble molecules and small (molecular weight less than 100 Da) nonionized water molecules cross fairly readily, and larger water-soluble molecules cross less easily [23]. Current iodinated nonionic monomeric contrast media and gadolinium contrast agents are water soluble with molecular weights in the range 500–850 Da. They would therefore be expected to cross into the fetus but less readily than smaller water-soluble molecules. This hypothesis is supported by the very small amounts of iobitrol, a nonionic iodinated contrast medium, which were shown to cross the rabbit placenta in the 24 h after injection [24].

Gadolinium agents have been shown in the placenta following intravenous administration to the mother both in animals and in clinical practice. In rabbits the highest placental gadolinium concentration occurred 5 min after gadopentetate dimeglumine injection with a decrease by 50% at 60 min [25]. Similarly in rats the highest placental concentration (18–30% of the injected dose) was seen at the end of the injection. There was a decrease of about 100-fold by 24 h, with the majority of this occurring in the first 4 h [26]. In 11 women between 16 and 37 weeks of pregnancy, gadolinium uptake into the placenta following a dose of 0.1 mmol/kg body weight of gadopentetate dimeglumine was sufficient for placental imaging [27].

Iodinated contrast media within the fetus

Distribution and excretion

Iodinated contrast media which traverse the placenta and enter the fetal blood may then be excreted by the kidneys into the bladder and so reach the amniotic fluid. Amniotic fluid which is swallowed enters the gut. Alternatively it has been suggested that contrast media may pass directly from the maternal blood to the amniotic fluid and thence to the

gut [28]. Bourrinet et al. [24] estimated that only 0.003% of the injected dose of iohexol and iobitrol reached fetal blood in the rabbit.

In man, a neonatal pyelogram following administration of an intravenous ionic agent prenatally to the mother was first described in 1963 [29]. Intravenous sodium diatrizoate (120 ml of Renografin, concentration not stated) was given to two pregnant women with impaired renal function (creatinine levels 132 and 176 $\mu\text{mol/l}$). Abdominal radiographs of their babies at 4 and 1–2 days after contrast medium injection showed opacification of the small and large bowel [30]. In impaired renal function the plasma contrast medium concentration in the mothers would remain high longer than in individuals with normal renal function with the possibility for more contrast medium to cross the placenta. In one woman who had intravenous urography with the ionic agent sodium iothalamate (dose not stated) 24 h before amniocentesis, the total iodine concentration in amniotic fluid was 380 $\mu\text{g/ml}$, much higher than in normal subjects ($4.4 \pm 1.6 \text{ ng/ml}$). In another woman, in whom amniocentesis was not done until 22 days after urography, the amniotic fluid iodine level was 29 ng/ml , suggesting that contrast media diffuse out into the mother through the placenta, as well as diffusing into the fetus [31]. Following the nonionic agent iohexol given to a pregnant woman for angiography, there was opacification of the intestine of her twin neonates [32]. Contrast media injected into the amniotic fluid directly the day before intrauterine transfusion also subsequently opacified the fetal gut [33].

Potential harmful effects

Thyroid

Depression of fetal thyroid function is the most important potential harmful effect of iodinated contrast media within the fetus. By 12 weeks the fetal thyroid is synthesizing thyroxine (T_4) under the influence of thyroid stimulating hormone (TSH). From 30 weeks onwards, serum triiodothyronine (T_3) levels increase to the time of birth. The fetal pituitary–thyroid axis is considered to be independent of the mother [34]. At delivery, TSH rises rapidly to peak at 30 min and then declines over the next 48 h. At the same time T_3 and T_4 levels increase and usually return to normal by 2 weeks [35–37]. Fetal thyroid function is important for normal development of the central nervous system [38, 39]. Medicines containing iodine are generally considered to be contraindicated in pregnant women because of the possibility of iodide uptake by the fetal thyroid leading to fetal hypothyroidism [23].

Amniography using both Lipiodol (iodized ethyl esters of the fatty acids of poppy seed oil) and meglumine diatrizoate injected into the amniotic fluid was associated with

markedly elevated TSH levels of 27–51 $\mu\text{U/ml}$ (normal 12 $\mu\text{U/ml}$) in six of seven neonates at 5 days. In only three of these was the cord TSH increased at birth. Subsequently, two of the babies developed hypothyroidism which was satisfactorily treated with thyroxine, and thyroid failure was suspected in a third baby whose clinical symptoms responded to thyroxine [2]. Amniography using water- and lipid-soluble contrast medium 4 days before delivery was associated with hypothyroidism in another infant [40]. The Lipiodol used for amniography is deposited on the vermix and then can be absorbed by the fetus over a prolonged period of time. Lipiodol given intramuscularly persists in the body for a long period and is used as a treatment for iodine deficiency including iodine deficiency in pregnancy. It results in urinary iodine levels above baseline for more than 12 months [41]. In rabbits, Lipiodol crossed the placenta and accumulated in the fetal thyroid [42].

Amniography using only the water-soluble agent meglumine diatrizoate injected into the amniotic fluid was associated with no significant change in cord blood T_4 and T_3 levels in 28 subjects compared to 25 controls [28]. However, later samples were not obtained. In pregnant women who have had intravenous urography, high amniotic fluid iodine levels were detected 24 h after intravenous contrast medium, but had declined by 22 days [31]. This led to the hypothesis that contrast media may traverse the placenta in both directions and therefore may be excreted by the mother. Water-soluble contrast agents such as meglumine diatrizoate only contain relatively small amounts of free iodide, and it is this substance which is potentially harmful to the fetal thyroid. The permitted upper level of free iodide in contrast medium of concentration 300 mg I/ml is below 50 $\mu\text{g/ml}$ immediately after production and below 90 $\mu\text{g/ml}$ after 3–5 years. Usually the free iodide concentration is less than one tenth of these amounts [43]. If 150 ml of contrast medium (300 mg I/ml) is used, for example for CT pulmonary angiography in a pregnant woman, and the free iodide content is 50 $\mu\text{g/ml}$, the total dose of free iodide is 7,500 μg . There is no experimental data to indicate how much of this free iodide crosses the placenta, how long it remains in the fetus, or what its effect on the fetal thyroid might be. The likelihood is that free iodide in the fetus diffuses out across the placenta rapidly and the fetal thyroid is only exposed for a short period of time. In women with impaired renal function, exposure of the fetus is likely to be for longer because blood levels of contrast medium or free iodide remain higher for longer.

In the neonate, high doses of nonionic contrast agents given intravenously do not appear to upset thyroid function. Thus in ten neonates aged 10–28 days who had received 1,500 mg I/kg of iopamidol, no abnormality in thyroid function could be detected at 10 and 30 days after the study [44].

Other

There is very little information about other adverse effects of iodinated contrast media in pregnancy. No adverse effects were noted in reports from 20 to 30 years ago when arteriography and amniography were practised [33, 45, 46]. The risks which occur in the general adult population are to be expected.

Conclusion

Fetal exposure to iodinated contrast medium and any associated free iodide is likely to be relatively short-lived. It is standard pediatric practice to screen all infants for hypothyroidism during the 1st week using a blood test [47]. Where the mother has received iodinated contrast medium during pregnancy, it is essential to ensure that this check is undertaken (Savage, personal communication, 2004). In view of the paucity of information in the literature, collection and publication of neonatal thyroid function results after maternal exposure to iodinated contrast media would be most helpful.

Gadolinium contrast agents during pregnancy

Distribution and excretion

The similarities in handling of iodinated intravascular contrast media and gadolinium MR agents suggest that the handling of gadolinium agents during pregnancy is likely to be similar to that of the iodinated agents.

Evidence of renal excretion of gadolinium by the fetus was obtained in rabbits in which renal concentrations of gadolinium increased between 5 and 60 min after gadopentetate dimeglumine 0.1 mmol/kg had been given intravenously to the mother. Gadolinium concentrations in other organs remained low [25]. The concentrations of gadolinium in the fetal kidney were theoretically high enough for MR imaging.

Following 0.3 mmol/kg of ¹⁴C-labeled gadodiamide injected intravenously, the highest gadolinium concentrations in the rat fetus were 170 times less than those in maternal plasma. At 4 h only 0.01% of the dose was present in the fetus, and only traces were present at 24 h [26]. This suggests back diffusion across the placenta and excretion by the mother may well occur as is considered likely with the water-soluble iodinated radiographic agents.

Safety

No adverse effects in the fetus have been documented when gadolinium agents have been given intravenously for MR studies during pregnancy. Gadopentetate dimeglumine 0.2

mmol/kg given in the 1st month of pregnancy inadvertently and gadopentetate dimeglumine given to two women at 3 and 5 months of pregnancy to diagnose Crohn's disease were not associated with subsequent fetal abnormality [48, 49]. In 11 women at 16–37 weeks gestation, gadopentetate dimeglumine (0.1 mmol/kg) used to image the placenta was not associated with adverse effects on the fetus [27]. In 11 women at 19–34 weeks of gestation who had MR excretory urography (gadopentetate dimeglumine 0.1 mmol/kg) there were no detectable adverse effects on the resultant infants [50]. In all gadolinium contrast agents the gadolinium is in a chelated form to minimize toxicity. Nonetheless, small amounts of free gadolinium may remain in animals following the use of these agents [51, 52]. In patients with severely reduced renal function (<10 ml/min) no free gadolinium was measured in the blood by plasma-atomic emission spectroscopy and by high-performance liquid chromatography on 5 consecutive days after administration of the contrast medium [53].

Drug excretion in milk

Drugs enter milk by one of two routes. The route through the alveolar cells involves transit through cell membranes. For water-soluble, low molecular weight drugs this is achieved when the molecules, surrounded by protein, pass through water-filled pores into the cells. The alternative route is through the intercellular clefts [54]. The concentration of drugs in milk is easier if the drug has a high affinity for binding to plasma and milk proteins. Nonionized drugs with low lipid solubility are absorbed slowly across lipid membranes [54]. These general concepts suggest that iodinated contrast media and gadolinium MR agents which are water soluble with minimal protein binding are likely to be secreted into milk with difficulty.

Iodinated contrast media

The potential risks to the baby are unknown. Measurements of iodinated contrast media in milk following intravenous and intrathecal water-soluble agents have shown very low levels of excretion in milk. Following 50 ml of intravenous ionic contrast media (sodium and meglumine iodamide and sodium and meglumine diatrizoate) in two lactating mothers, no detectable contrast medium excretion in milk was found up to 16 h using spectrophotometric analysis [55]. With larger doses (350 mg I/kg) of iohexol in four women and metrizoate in two women, low levels of contrast medium excretion in milk were detected using liquid chromatography [56]. Nielsen et al. [56] calculated that with a milk intake of 0.15 l/kg per day, the infant would have received 1.7 mg I/kg with iohexol and 0.78 mg I/kg with metrizoate. This corresponds to 0.5% of the maternal dose with iohexol and 0.3% of the maternal dose with metrizoate. Following

Table 1 Simple guidelines on the use of iodinated and gadolinium contrast media during pregnancy and lactation

	Iodinated agents	Gadolinium agents
Pregnancy	(a) In exceptional circumstances, when radiographic examination is essential, iodinated contrast media may be given to the pregnant mother (b) Following administration of iodinated agents to the mother during pregnancy, thyroid function should be checked in the neonate during the 1st week	(a) When MR examination is necessary, gadolinium media may be given to the pregnant mother (b) Following administration of gadolinium agents to the mother during pregnancy, no neonatal tests are necessary
Lactation	Breast-feeding may be continued normally when iodinated agents are given to the mother	Breast-feeding may be continued normally when gadolinium agents are given to the mother
Pregnant or lactating mother with renal impairment	No additional precautions are necessary for the fetus or neonate. Follow ESUR guidelines for contrast media administration when renal function is impaired	No additional precautions are necessary for the fetus or neonate. Follow ESUR guidelines for contrast media administration when renal function is impaired

metrizamide (5.06 mg) given intrathecally, only 0.02% of the dose was excreted in the milk by 44 h [57]. Even after fat-soluble cholecystographic agents, iodine excretion in the milk was very low [58]. Furthermore, only very small amounts of the iodinated contrast agents which enter the gut in milk are absorbed into blood. Thus when the non-ionic agent metrizamide was used as an oral contrast agent, only 0.4% was excreted in the urine in the 1st day, and a total of 0.8% by the end of the 3rd day [59]. The recommended dose of iohexol for pediatric urography is 900 mg I/kg for babies under 6.5 kg, and 600 mg I/kg for babies 7.0 kg or more [60]. The oral dose of iohexol received in 24 h by the baby in the milk after a maternal dose of 350 mg I/kg has been estimated to be 1.7 mg I/kg, which is 0.002% of the maximum dose recommended to be given intravenously for urography [56, 59]. The likelihood of either direct toxicity or allergic reaction is therefore extremely low. As with other drugs and foodstuffs, the taste of milk may be altered if contains contrast medium.

Gadolinium MR agents

Very low levels of gadolinium contrast medium are detected in the milk after intravenous administration. In 20 lactating women given gadopentetate dimeglumine (0.1 mmol/kg in 19, and 0.2 mmol/kg in 1) the cumulative gadolinium excretion in milk over 24 h was less than 0.04% of the intravenous dose ($0.57 \pm 0.71 \mu\text{mol}$) [3]. In a lactating woman who received gadopentetate dimeglumine (0.1 mmol/kg) the cumulative excretion of gadolinium was 0.011% of the total dose given [61]. In another lactating woman who received the same dose of gadopentetate dimeglumine the cumulative gadolinium excretion was 0.023% of the administered dose over 24 h [62].

When gadolinium contrast agents enter the gut, only very small amounts are absorbed. Thus, gadopentetate dimeglu-

mine (0.005 or 0.01 mmol/kg) used as an oral contrast agent with mannitol in adults was not associated with a change in signal intensity of the urine after contrast medium, indicating significant gadolinium absorption was unlikely [63]. The recommended pediatric dose of gadolinium agents is 0.1–0.2 mmol/kg, and this is well tolerated in infants less than 6 months [64, 65]. The amount of gadolinium agent in the gut of a breast-fed infant after gadolinium has been given intravenously to the mother is less than 1% of the recommended intravenous dose for the infant [3]. In all gadolinium agents the gadolinium is chelated to minimize toxicity. Nonetheless, small amounts of free gadolinium may remain in animals following the use of these agents. Again, the taste of the milk may be altered if it contains gadolinium contrast medium.

Conclusion

The amounts of both iodinated and gadolinium agents likely to reach the neonatal circulation from the milk when a lactating mother is given either type of agent intravascularly are very small. They are significantly less than the amounts which may be administered to neonates during imaging procedures. The extremely low risk to the neonate from the contrast medium may therefore not be considered sufficient to warrant the potential disruption to both the mother and the baby by ceasing breast-feeding for 24–48 h after contrast medium. Based on this review, guidelines (Table 1) have been proposed and approved at the 11th European Symposium on Urogenital Radiology.

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