

J – General antimicrobics for systemic use

J01AA – Tetracyclines

These broad-spectrum antibiotics, mainly bacteriostatic agents, inhibit protein synthesis of ribosomes.

Doxycycline – J01AA02

Patented in 1962.

Chlortetracycline – J01AA03

Patented in 1950

Lymecycline – J01AA04

Patented in 1962

Methacycline – J01AA05

Patented in 1961

Tetracycline – J01AA07

Patented in 1955

Minocycline – J01AA08

Patented in 1964.

Case report

- The early reports on subjects showing anomalous color of deciduous teeth, exposed to tetracyclines in the first trimester of pregnancy, date back to 1956 (Schwachman and Schuster 1956). They were later confirmed by similar case reports (Cohlan et al 1961, Harcourt et al 1962, Davies et al 1962, Rendle-Short 1962) and followed afterwards by a far large number of other reports. Preterm offspring exposed in the 2nd and 3rd trimester (Renle-Short 19162), Cohlan et al 1963, Kline et al 1964, Kutscher et al 1966) were reported to show a slower bone development, especially relevant to the tibia.
- Thomson 1962): 1 newborn exposed to tetracycline in the first trimester had reduced upper limbs.
- Harley et al (1964): 3 of the 8 newborns with congenital or infant cataract were exposed to tetracycline and 1 of them to oxytetracycline during the first trimester.
- Farrar and Mackie (1964): 1 newborn showing congenital cataract was exposed to tetracycline in the first trimester.

Retrospective cohort studies with internal controls

- Aselton et al (1985), Seattle GHC: of 174 first trimester exposures, 2 newborns had non-specified congenital anomalies (1.14%). RR = 0.7 (CI 95%: 0.2-2.9).
- Rosa (1993), Michigan MSS: of 1,795 first trimester exposures to doxycycline, 78 newborns had major defects, 76 expected (RR = 1.0; CI 95%: 0.8-1.3). Of 1,004 first trimester exposures to tetracycline, 47 newborns had major defects, 43 expected (RR = 1.1; CI 95%: 0.8-1.5). Of 181 first trimester exposures to minocycline, 8 newborns had major defects, 7 expected (RR = 1.1; CI 95%: 0.5-2.3).

Prospective cohort studies with internal controls

- Heinonen et al (1977), CPP: 341 exposures in the early 16 weeks of pregnancy. ARR for any type of malformations = 0.9 (CI 95%: 0.6-1.5), for major malformations = 0.6 (CI 95%: 0.2-1.2), for minor malformations = 1.7 (CI 95%: 0.8-3.0).

Case-control studies, nonspecific

- Czeizel and Rockenbauer (1977), Hungarian CCSCA (1980-1992): 18,515 newborns with congenital anomalies. 32,804 healthy newborns. 56 cases exposed to doxycycline vs. 63 controls. OR = 1.3 (CI 95%: 1.1-1.6). Memory bias or multiple control effect is not to be excluded.

Case-control studies, specific

- Saxen (1975) Finnish RCM: a study on 599 cases of cleft lip/cleft palate, and 590 controls matched as per main confounding variables (place of birth, maternal residence and interviewer aware of the status of the case or control). The survey was carried out on both tetracyclines and chloramphenicol together and only one OR for first trimester exposures has been observed for cleft lip/cleft palate (not for cleft palate) = 3.8 (CI 95%: 0.97-21.3). The author suggests that such an association may depend on the confounding outcome of the fever, which was more frequent in cases.
- Rothman et al (1979): 390 newborns with congenital cardiopathies, 1,254 healthy controls to assess the association with the exposure to various drugs. OR for first trimester exposure to tetracycline based on 8 cases = 3.3 (CI 90%: 1.4-7.6). Authors themselves interpreted this result as probably due to recall bias and/or the confounding factor of the original illness.
- Zierler and Rothman (1985): 298 newborns with congenital cardiopathies, 5 of whom exposed. 738 healthy controls, 6 of whom exposed. OR for cardiopathy in general during the first trimester = 2.1 (CI 90%: 0.7-5.8). A specific association, probably due to multiple analysis, was noticed with TGV based on just 3 cases.
- Medveczky et al (2004), Hungarian CCSCA: of 1,202 newborns with DTN, 6 exposed to oxytetracycline in the 2nd month of gestation (critical stage for DTN). 38,151 healthy controls, 23 of whom exposed, having OR = 7.2 (CI 95%: 2.9-17.9). 22,475 pathologic controls – with every other congenital anomaly – among whom 38 exposed, having OR = 2.6 (CI 95%: 1.1-6.2). This outcome is based on just 6 cases and the comparison between the OR of healthy controls and the OR of pathological controls suggests a memory bias. The result obtained when matched with pathological controls is barely significant and it may be influenced by the high number of multiple matching carried out in this study (77 drugs or groups of drugs).

Nested case-control studies, specific in the prospective cohort of all newborns

- Kallen and Otterblad Olausson (2003), Swedish MBR: cases = 5,015 newborns with cardiovascular defects, among whom 11 exposed to tetracyclines in the first trimester; 577,730 controls, among whom 1,190 exposures. OR for cardiovascular defects = 1.1 (CI 95%: 0.6-1.9).

Conclusions: Several clinical reports point out that the exposure to tetracycline after the third trimester (since week 13 following conception) affects the color of deciduous teeth, which appear yellowish and even darker: brown or gray-brown. At the light of Wood lamp they have the typical fluorescence. Alterations are related to the type of tetracycline, its dosage, the length of treatment and the stage of teeth calcification at the moment of exposure (Cohlan 1977). In case of exposure to tetracyclines in the last period of pregnancy also the crown of permanent teeth may possibly be stained (Baden 1970). The altered coloring of teeth is not causative of dental caries and it does not affect their adamantine layer (Genot et al 1970, Rebich et al 1985), it is just a cosmetic issue. Tetracyclines also affect bone development, little evident, though, and not remarkable from the clinical viewpoint. Tetracyclines should not be prescribed during the 2nd and 3rd trimester of pregnancy.

The activity of this side effect is well known. Tetracyclines, being strong chelating agents, leave a fluorescent compound on teeth during calcification and on developing bones. Teeth start their calcification at the end of the 4th month of gestational age. As far as other congenital anomalies are concerned: a) some case reports hypothesize an increased risk of cataract also during first trimester exposures. Such a hypothesis cannot be totally excluded both because of the mentioned yellowish deposit on crystalline lens (Krejci and Brettschneider 1983), and because of the analogous study on rats exposed during pregnancy (Krejci et al 1980). b) Rothman raised the hypothesis of increased risk of cardiopathies (maybe biased by memory) and Rothman and Zierle suggest the same thing also relevant to TGV (it comes out from multiple matching). Such a hypothesis has not been confirmed by a subsequent study, which was anyway only based on 11 exposures, and it deserves to be further surveyed.

J01BA – Amfenicols

Cloramphenicol – G01AA05 – J01BA01 – S01AA01

This natural antibiotic has bacteriostatic activity. Plasma concentrations in fetus are 25-100% the maternal ones. Patented in 1949.

Case-control studies, nonspecific

- Czeizel et al (2000), Hungarian CCSCA: 22,865 newborns with congenital anomalies, 38,151 healthy newborns. 52 exposures (0.23%) throughout pregnancy among cases vs. 51 (0.13%) among controls. AOR for exposures throughout pregnancy = 1.7 (CI 95%: 1.1-2.6). The analysis carried out as per subgroups of exposures (1st month, 2nd-3rd month and 2nd-3rd trimester) has not changed the values of AOR that suggests, also according to the author, a recall bias effect. To put it plainly, the study is to be considered negative.

Case-control studies, specific

- Saxen, (1975), Finnish RCM: a study on 599 cases of cleft lip/palate and 590 controls matched as per main confounding variables (birth place, maternal residence and interviewer aware of the status of the case or control). The survey was carried out on both tetracyclines and chloramphenicol together and only one OR for first trimester exposures has been observed for cleft lip/palate (not for cleft palate) = 3.8 (CI 95%: 0.97-21.3). The author suggests that such an association may depend on the confounding outcome of the fever, which was more frequent in cases.

Prospective cohort studies with internal controls

- Heinonen et al (1977), CPP; 98 exposures in the early 16 weeks, 5 newborns with congenital anomalies (ARR = 1.1; CI 95%: 0.5-2.7)

Feto-neonatal effects: The use of this drug at various stages of pregnancy has not caused adverse outcomes in the fetus (Ravid and Roaff 1972, Conningham et al 1973, Schiffman et al 1977). 1 newborn with “gray baby syndrome” was reported in literature, exposed in the last period of pregnancy (Oberheuser 1971)

Conclusions: The available studies concerning third trimester exposures have not identified an increased population-based reproductive risk. ADEC considers chloramphenicol, when strictly necessary, a drug of choice in pregnancy. The possibility of the gray baby syndrome in the newborn exposed at the end of pregnancy should be seriously considered on the base of the following issues. a) Chloramphenicol is readily transferred across the placenta, b) such a side effect is clearly shown in the newborn, and c) one report has described the gray baby

syndrome due to exposure in the last period of pregnancy. The use of chloramphenicol is therefore not recommended in the third trimester of pregnancy.

Thiamphenicol – J01BA02

This is a meta-sulfonic derivative of chloramphenicol. Patented in 1955.

We have been unable to locate references on possible human reproductive effects of this agent.

Studies on laboratory animals

- Suzuki et al (1973): nonteratogenic in mice or rats at doses 1-33 and 1-3 times higher than the regular human dose, respectively.
- Silva and Andrade (1970): bone malformations have been reported in rats at doses twice the human clinical doses.

Conclusions: There is no written evidence of specific studies concerning the use of thiamphenicol in human pregnancy. Being an analog of chloramphenicol, we may come to similar conclusions.

J01C – Beta-lactam antibacterial drugs, penicillins

The following studies have studied penicillins and/or their derivatives, with no specification.

Prospective cohort studies with internal controls

- Kullander and Kallen (1976): a study on 5,753 infants. 194 newborns had major congenital anomalies: 5 exposures to penicillin derivatives (as expected), 3 of which showing hypospadias while 0.7 was expected (RR = 4.3; CI 95%: 0.9-12.5), 1 dysplasia of the hip and 1 multiple malformations.
- Heinonen et al (1977), CPP: 3,546 exposures to derivatives of penicillin in the early 16 weeks of gestation. ARR for any type of malformation = 0.9 (CI 95%: 0.8-1.1), ARR for malformation syndromes, except for Down syndrome = 1.7 (CI 95%: 0.9-2.9), ARR for cardiopathies (29 cases) = 1.0 (CI 95%: 0.7-1.4).

Case-control studies, specific

- Saxen (19175), Finnish RCM: 599 children with isolated cleft lip +/- cleft palate. 590 healthy controls. A significant increase in the use of penicillins has been reported ($p < 0.05$) in the first trimester of gestation, in those cases where facial schisis was associated to another defect (see Table). The result can be interpreted as the effect of multiple matching, retrospective analysis, or as the confounding outcome of the original illness and/or hyperthermia.

Exposure	Isolated cleft palate % case/control	Isolated cleft lip +/- cleft palate % case/control	Cleft lip +/- cleft palate with associated defects % case/control
1 st trimester	6,5 / 4,4	9,9 / 5,7	9,7 / 2,3 p<0.05
2 nd trimester	5,2 / 4,9	3,0 / 4,8	3,0 / 4,6
3 rd trimester	1,3 / 2,2	3,5 / 2,6	3,0 / 3,0

- Winship et al (1984): 764 newborns with NCS congenital anomalies, 764 healthy newborns. OR as per exposure to penicillin derivatives in the first trimester = 0.8 (CI 95%: 0.5-1.2).

Nested case-control studies, specific in the prospective cohort of all newborns

- Kallen and Otterblad Olausson (2003), Swedish MBR: 5,015 cases of newborns showing cardiovascular defects and among them 103 exposures to penicillins in the first trimester. 577,730 healthy controls and among them 12,417 exposures. OR as per CVS defects = 1.0 (CI 95%: 0.8-1.2).

J01CA – Broad-spectrum penicillins

These bactericidal antibiotics share the nucleus of 6-aminopenicillanic acid (6-APA). Natural penicillins are produced by several species of molds. Synthetic penicillins can be obtained changing the lateral chain of G penicillin, the sole natural compound currently marketed.

Prospective cohort studies without controls

- Colley et al (1983): 284 first trimester exposures to ampicillin or amoxicillin have not revealed an increased number of congenital anomalies.

Case-control studies, specific

- Shaw et al (1988), California BDMR: 538 newborns with DTN, 539 healthy newborns. 13 cases exposed to ampicillin or amoxicillin, vs. 16 controls OR = 0.81 (CI 95%: 0.4-1.7).

Ampicillin – J01CA01 – J01CR01- J01CR50 – S01AA19

This semi-synthetic penicillin is an amino-penicillin. Patented in 1960.

Case-control studies, nonspecific

- Czeizel et al (2001) Hungarian CCSCA: 22,865 newborns with congenital anomalies, 38,151 healthy newborns. 1,643 exposed cases vs. 2,632 controls. OR = 1.0 (CI 95%: 0.7-1.2).

Retrospective cohort studies with internal controls

- Jick et al (1981), Seattle GHC: 309 first trimester exposures. 4 newborns (1.3%) with unspecified congenital anomalies. RR = 1.1 (CI 95%:0.4-3.0)
- Aselton et al (1985), Seattle GHC: 409 first trimester exposures. 3 newborns (0.7%) with unspecified congenital anomalies. RR = 0.4 (CI 95%: 0.1-1.3).
- Rosa (1993), Michigan MSS: 10,011 first trimester exposures. 441 newborns with congenital anomalies, 426 expected. RR = 1.0 (CI 95%: 0.8-1.2).

Case-control studies, specific

- Rothman et al (1979): 390 newborns with congenital cardiopathies, 1,254 healthy controls to assess an association with the exposure to various drugs. OR = 3.3 (CI 90%: 1.3-8.1). The authors themselves believe that this result may be due to the recall bias and to the confounding factor of the original infectious disease or to hyperthermia.
- Zieler and Rothman (1985): 298 newborns with congenital cardiopathies, 9 of which exposed; 738 healthy controls, 19 of which exposed. OR = 1.2 (CI 90%: 0.6-12.3). The study was carried out by the same group that had previously identified an association (See above).
- Bracken (1986): 330 newborns with congenital anomalies, 3,002 controls chosen randomly among the population. OR = 0.8 (CI 95%: 0.3-2.3). 27 cases with transposition of the great vessels OR = 5.4 (CI 95%: 1.2-23.4) that increased to 12.0 (CI 95%: 1.6-89.1) if matched with controls showing other congenital cardiopathies. The result may be due to multiple matching or to the confounding factor of the original disease and/or hyperthermia.
- Perez-Molina et al (2002): a study carried out in a single hospital in Mexico between 1989 and 1997. 166 cases of newborns with neural tube defects

(107 high and 59 low NTD); 166 control infants with no evident malformations, born right after the index case and matched as per sex. Various drugs were taken in consideration for the exposure evaluation, collected routinely and retrospectively (at birth) with a closed-answers questionnaire. 14 cases exposed to penicillin vs. 3 among controls: OR = 8.5 (CI 95%: 2.1-39.2). An association between NTD with upper respiratory infection and paracetamol was detected; no minimization, no evaluation of memory and interview bias (result evaluation more acceptable).

Neonatal effects: Despite the lack of side effects in two randomized studies (Svare et al 1997, Wing et al 1998), the use of ampicillin (like other antibiotics) in the period immediately preceding birth may increase the risk of neonatal infections from bacteria resistant to usual antibiotics (Joseph et al 1998). Like amoxicillin it may increase the risk of necrotizing enterocolitis (See amoxicillin).

Amoxicillin – J01CA04 – J01CR02

This semi-synthetic penicillin is an amino-penicillin and analog of ampicillin. Patented in 1962.

Case-control studies, nonspecific

- Czeizel et al (2001), Hungarian CCSCA: 6,935 newborns with congenital anomalies, 10,238 healthy newborns. OR for exposure to amoxicillin+clavulanic acid in the first trimester = 1.4 (CI 95%: 0.9-2.0). No association was observed for specific malformations (i.e.: cleft lip/palate, polydactyly, CHD, diaphragm anomalies and hypospadias).

Retrospective cohort studies with internal controls

- Rosa (1993), Michigan MSS: of 8,538 first trimester exposures, 317 newborns had major defects, 363 expected. RR = 0.9 (CI 95%: 0.7-1.0)
- Jespen et al (2003), PEP Database North Jutland: 401 exposures at non-specified stages of pregnancy. 10,237 not exposed women. OR for exposure to amoxicillin: low birth weight = 0.6 (CI 95%: 0.3-1.5), preterm delivery = 0.8 (CI 95%: 0.5-1.2), congenital anomalies = 1.2 (CI 95%: 0.5-2.5), miscarriage = 0.9 (CI 95%: 0.7-1.2).

Feto-neonatal effects: No adverse effect in exposures at various stages of pregnancy for maternal gonorrhoea (Cavenee et al 1993). An increased risk of necrotizing enterocolitis was reported for exposure in the last period of pregnancy (Jenyon et al 2001, 2002, Grantham et al 2002).

Bacampicillin – J01CA06

This semi-synthetic penicillin is an amino-penicillin and ampicillin ester. It is hydrolysed as ampicillin in the gastroenteric tract. Patented in 1975.

Retrospective cohort studies with internal controls

- Rosa (1993), Michigan MSS: of 30 first trimester exposures, 2 newborns had major defects, 1 expected. RR = 2.0 (CI 95%: 0.2-7.2).

Mezlocillin – J01CA10

This semi-synthetic penicillin was patented in 1971

No specific studies have been located in literature consistent with its use in human pregnancy.

Studies on laboratory animals

- Hamada and Imanishi (1978): nonteratogenic in rats and macacus rhesus treated with 1 and 1-3 times respectively the dose used in humans.
- Tanioka and Koizumi (1978): nonteratogenic in macacus rhesus (100mg/kg).

Piperacillin – J01CA12

This is a semi-synthetic ureidopenicillin. Patented in 1978.

No specific studies have been located in literature consistent with its use in human pregnancy.

Studies on laboratory animals

Takai et al (1977): nonteratogenic neither in mice (2,000-mg/kg e.v.) nor in rats (1,000 mg/kg).

Class J01CA conclusions: The available studies on broad-spectrum penicillin agents, in particular ampicillin and amoxicillin, do not show an increment in the reproductive risk. Ampicillin has been commonly used for years. ADEC, FASS and WGZ consider it a drug of choice in pregnancy. An analysis with specific study patterns should be carried out on the hypothesis of an association with increased specific cardiac defects, or with NTD. This is in fact, by now, to be interpreted as a memory bias effect or the bias of the infectious disease and/or of hyperthermia, both acting as a confounding factor.

None of the drugs belonging to this class suggest an increase in population background risk in case of exposure. This, in consideration of the acquired data on ampicillin and amoxicillin - both widely tested and considered drugs of choice - and despite the absence of reported anomalies over the long period of commercialization. Besides, no teratogenic effects in laboratory animals have been found (records provided by manufacturer for registration, not available in databases).

J01CE – Beta-lactamase sensible Penicillins

Benzyl penicillin (Penicillin G) – J01CE01

This is a natural penicillin, deriving from “penicillum notatum”, the first antibiotic found by Fleming in 1928. Used in medicine since 1941.

Benzathine benzyl penicillin - J01CE08

Retard preparation of Penicillin G. Available in Italy since 1950.

Cohort studies with internal controls

- Jick et al (1981), Seattle GHC: 349 exposures during the first trimester, 6 newborns with unspecified congenital anomalies (1.7%); RR = 1.0 (IC 95%: 0.5-2.1).
- Aselton et al (1985), Seattle GHC: 297 exposures during the first trimester, 2 newborns with unspecified congenital anomalies (0.7%); RR = 0.4 (IC 95%: 0.1-1.7).

Cohort prospective studies with internal controls

- Dencker et al (2002), PEP Database North Jutland: 131 infants exposed to phenoxymethylpenicillin alone during the first trimester were matched with 9,236 infants who had not been exposed. OR = 1.4 (IC 95%: 0.6-3.1). The analysis was made only for cardiovascular defects (9 exposures) and it uncovered AOR=1.7 (IC 95%: 0.8-3.7).

Case-control studies, nonspecific

- Czeizel et al (2001), Hungarian CCSCA: 22,865 newborns with congenital anomalies, 38,151 healthy newborns. 173 exposures among the cases vs. 218 controls. OR = 1.3 (IC 95%: 1.1-1.6). The recall bias is at the base of this outcome. This is also in the author's opinion.

Case-control studies, specific

- Shaw et al (1998), California BDMP: 538 newborns with neural tube defect. 539 healthy controls. 9 exposures among the cases, vs. 10 controls: OR = 0.9 (IC 95%: 0.4-2.2).

Nested case-control studies, specific in the prospective cohort of all newborns

- Kallen (2003), Swedish MBR: 1,044 newborns with non-syndrome oral schisis, 29 of which exposed to penicillin V; controls (total of newborns): 576,873 among whom 18,494 were exposed. AOR = 0.9 (IC 95% 0.61.3).
- Kallen and Otterblad Olausson (2003) Swedish MBR: 5,015 newborns with cardiovascular defects, 57 of whom exposed to penicillin during the first trimester, 577,730 controls, 7,923 of whom exposed. OR per cardiovascular defects = 0.8 (IC 95%: 0.6-1.1).

Conclusions: Despite the presumably widespread use of penicillin, there are quite few available studies. An increase in the background reproductive risk has not been shown, and is not even likely, considering the lack of reported anomalies over the long period of commercialization. ADEC, FASS and WGZ consider benzil penicillin a drug of choice in pregnancy.

J01CE – Beta-lactamase resistant penicillins

Cloxacillin – J01CF02

This is semi-synthetic isossazolil penicillin. Patented in 1960.

Retrospective cohort studies with internal controls

- Rosa (1993), Michigan MSS: 46 exposures during the first trimester, 3 newborns with major defects, 2 expected: RR = 1.5 (IC 95%: 0.3-4.4).

Oxacillin – J01CF04

This is semi-synthetic isossazolil penicillin. Patented in 1961.

Case-control studies, nonspecific

Czeizel et al (2001), Hungarian CCSCA: 22,865 newborns with congenital anomalies, 38,151 healthy newborns. 14 exposures among cases vs. 19 controls: OR = 1.2 (IC 95%: 0.62.6)

Flucloxacillin – J01CF05

This is semi-synthetic isossazolil penicillin. Patented in 1966.

We have been unable to locate references on possible human reproductive effects of this agent, or have we found any similar studies on laboratory animals.

Class J01CF conclusions: The studies located in literature, consistent with the use of some of the drugs belonging to this therapeutic class are limited or totally absent. In case of exposure an increase in the background reproductive risk is not likely, due to their pharmacological characteristics. They are, in fact, analogous to other, more deeply studied penicillins. Besides, there is a lack of reported anomalies over the long period of commercialization and teratogenic effects in

laboratory animals have not been found (records provided by manufacturer for registration, not available in databases).

J01CR – Penicillin associations, including beta-lactamase inhibitors

These can be found in association with antibiotics, to increase their spectrum.

Sulbactam

Beta-lactamase inhibitor, available in association with ampicillin; see sultamicillin (J01CR04). It is available in Italy since 1987.

We have been unable to locate references on possible human reproductive effects of this agent.

Studies on laboratory animals

- Horimoto et al (1984): nonteratogenic in rats (500mg/kg).

Tazobactam

This is a Beta-lactamase inhibitor, available in association with piperacillin (see J01CA12). It is available in Italy since 1995.

We have been unable to locate references on possible human reproductive effects of this agent.

Studies on laboratory animals

- Sato et al (1994): nonteratogenic in rats (3,000 mg/dose).

Clavulanic acid

Beta-lactamase inhibitor produced by *Streptomyces Clavuligerus*. It is available in association with amoxicillin (see J01CA04) and ticarcillin (J01CR03). It is available in Italy since 1989.

Case-control studies, nonspecific

- Czeizel et al (2001), Hungarian CCSCA: 6,935 newborns with congenital defects, 10,238 healthy newborns. OR for exposure during the first trimester to the association amoxicillin+clavulanic acid = 1.4 (IC 95%: 0.9-2.0).

Retrospective cohort studies with internal controls

- Rosa (1993), Michigan MSS: 556 exposures during the first trimester (presumably in association with a penicillin), 24 newborns with major defects, 24 expected: RR = 1.0 (IC 95%: 0.6-1.5).

Ticarcillin – J01CR03

This is semi-synthetic bactericide penicillin effective against a broad spectrum of bacteria. It derives from the penicillin fundamental nucleus. It is available in Italy since 1991.

We have been unable to locate references on possible human reproductive effects of this agent.

Studies on laboratory animals

- Jackson et al (1985): nonteratogenic in neither mice nor rats.

Sultamicillin – J01CR04

This is made of sulbactam (irreversible beta-lactamase inhibitor) and ampicillin (see). It is available in Italy since 1990.

We have been unable to locate references on possible human reproductive effects of this agent, or have we found any similar studies on laboratory animals.

Class J01CR conclusions: The studies located in literature, consistent with the use of some of the drugs in this therapeutic class are limited or totally absent. In case of exposure an increase in the background reproductive risk is not likely, due to their pharmacological characteristics. Besides, there is a lack of reported anomalies over the long period of commercialization and teratogenic effects in laboratory animals have not been found (records provided by manufacturer for registration, not available in databases).

J01CR50 – Associations of penicillins

Dicloxacillin – J01CR50

This isosaxilpenicillin is a semi-synthetic penicillin,. It is available in association with ampicillin (see J01CA04). Patented in 1961.

Cohort retrospective studies with internal controls

- Aselton et al (1985), Seattle GHC: 86 exposures during the first trimester: 3 newborns with congenital anomalies, not specified (2.3%), RR = 1.4 (IC 95%: 0.4-5.7).
- Rosa (1993), Michigan MSS: 46 exposures during the first trimester, 1 newborn with major defects, 2 expected: RR = 0.5 (IC 95%: 0.01-2.8).

Conclusions: ADEC considers this a drug of choice in pregnancy. See penicillins.

J01DA – Cephalosporins and related drugs

These are antibiotics, effective against a broad spectrum of bacteria, all having in common the fundamental 7-amino-cephalosporanic acid (7Aca) nucleus, that is obtained by cephalosporin C. This, in turn, is a natural compound isolated from a mycete. They inhibit the synthesis of the bacterial cell wall. According to the synthesis period of the drug they are classified as of first, second and third generation.

Case-control studies, nonspecific

- Czeizel et al (2001) Hungarian CCSCA: Cases = 22,865 newborns with congenital anomalies; controls (a) = 38,151 healthy newborns, controls (b) = 812 newborns with Down syndrome. No association has been found between the many specific studied malformations and cephalosporins (i.e.: cefalexin, cefuroxime, cefaclor) administered during the 2nd and 3rd month of pregnancy. The association was uncovered only with clubfoot, but it disappeared when the analysis was restricted to the clinical documents alone, thus suggesting a memory bias.

Case-control studies, specific

- Hernandez-Diaz et al (2001), Boston SEUBDS: 1,242 cases of neural tube defects, 6,600 controls with malformations chosen among those unlikely to be prevented by folic acid. OR = 1.6 (IC 95%: 0.6-4.3) for exposures during the first two months after the latest menstruation. In a survey carried out of subgroups OR = 4.0 (IC 95%: 1.2-12.8) was seen for exposures to cefalexin, based on just 6 exposures. (According to the author the outcome is attributable to various other hypotheses, such as multiple matching and confounding factors – such as hyperthermia – and a lack of folic acid intake over the periconceptional period.

Nested case-control studies, specific in the prospective cohort of all newborns

- Kallen and Otterblad Olausson (2003), Swedish MBR: 5,015 cases with cardiovascular defects, 13 of which exposed to cephalosporin during the first trimester; 577,730 controls, among which 1,404 exposures. OR for CVS defects = 1.1 (IC 95%: 0.73-2.02).

Cefalexin – J01DA01

It is a cephalosporin of first generation. Patented in 1968.

Cohort studies with internal controls

- Rosa (1992), Michigan MSS: 3,613 exposures during the first trimester, 176 newborns with major defects, 154 expected: RR = 1.1 (IC 95%: 1.0-1.3). 11 oral schisis were seen, 5 expected. RR= 2.2 (IC 95%: 1.1-3.9).

Cefalotin – J01DA03

It is a cephalosporin of first generation. Patented in 1962.

We have been unable to locate references on possible human reproductive effects of this agent during pregnancy.

Studies on laboratory animals

- Ootaka et al (1979): nonteratogenic in rats, at 3-7 times exceeding the human therapeutic dose.
- Nomura et al (1984): increase in congenital anomalies and fetal death in mice, at 3-7 times exceeding the human therapeutic dose.

Cefazolin – J01DA04

It is a cephalosporin of first generation. Fetal levels are around 35-70% compared to those in the maternal serum. Patented in 1970.

We have been unable to locate references on possible human reproductive effects of this agent during the first trimester of pregnancy.

Studies on laboratory animals

- Birkhead et al (1973): nonteratogenic neither in mice (2,400 mg/kg) nor in rabbits (240 mg/kg).
- Hasegawa et al (1987): nonteratogenic in rats at 2-4 times exceeding (800 mg/kg) human therapeutic dose.

Feto-neonatal effects: administered in the second half of pregnancy with no adverse effects in offspring (Sanchez-Ramos et al, 1995).

Cefoxitin – J01DA05

It is a cephalosporin of second generation. Patented in 1971.

We have been unable to locate references on possible human reproductive effects of this agent.

Experimental studies on laboratory animals

- Watanabe et al (1978): nonteratogenic in rats or mice (400-900 mg/kg e.v.).

Cefuroxim – J01DA06

It is a cephalosporin of second generation. Patented in 1973.

Cohort retrospective studies with internal controls

- Rosa (1993), Michigan MSS: 143 exposures during the first trimester, 3 newborns with major defects, 6 expected: RR = 0.5 (IC 95%: 0.1-1.5).

Cohort prospective studies with internal controls

- Berkovitch et al (2000), TIS Israel: 106 exposures during the first trimester, 106 not exposed controls. Incidence of congenital anomalies among exposed newborns, 3.2 vs. 2% among controls: RR = 3.3 (IC 95%: 0.3-9.2).

Cefamandol – J01DA07

It is a cephalosporin of second generation. Patented in 1972.

We have been unable to locate references on possible human reproductive effects of this agent in the first trimester of pregnancy.

Studies on laboratory animals

- Wold et al (1978): nonteratogenic in rats or mice.

Cefaclor – J01DA08

It is a cephalosporin of first generation. Patented in 1975.

Cohort studies without controls

- Lilly Company (2002): 16 healthy newborns (chosen according to a prospective study) exposed during the first trimester of pregnancy. 23 exposures were chosen according to a retrospective study that uncovered the following. 2 VIP, 1 miscarriage, 1 stillbirth, 11 healthy newborns and 4 fetuses/born with congenital anomalies exposed during the first trimester (VIP for trisomy 13; VIP for growth delay; newborn with Poland syndrome; newborn with scoliosis), 4 newborns with congenital anomalies exposed after the first trimester.

Cohort retrospective studies with internal controls

- Rosa (1993), Michigan MSS: 1,325 exposures during the first trimester, 75 newborns with major defects, 56 expected: RR = 1.3 (IC 95%: 1.1-1.7). 8 oral schises were observed, 2 expected: RR= 4.0 (IC 95%: 1.7-7.9).

Cefadroxil – J01DA09

This is a cephalosporin of first generation. Patented in 1970.

Cohort retrospective studies with internal controls

- Rosa (1993), Michigan MSS: 722 exposures during the first trimester, 27 newborns with major defects, 30 expected: RR = 0.9 (IC 95%: 0.6-1.3).

Nested case-control studies, specific in the prospective cohort of all newborns

- Kallen and Otterblad Olausson (2003), Swedish MBR: 5,015 cases newborns with cardiovascular defects, 11 of which exposed to cefadroxil during the first trimester; 577,730 controls, 1,135 of which were exposed. OR for CVS defects = 1.1 (IC 95%: 0.6-2.0).

Cefotaxime – J01DA010

This is a cephalosporin of third generation. Patented in 1977.

We have been unable to locate references on possible human reproductive effects of this agent.

Studies on laboratory animals

- Sugisaki et al (1981): nonteratogenic in rats or rabbits (2,000-6,000 mg/kg e.v.).

Ceftazidime – J01DA011

This is a cephalosporin of third generation. Patented in 1981.

We have been unable to locate references on possible human reproductive effects of this agent.

Studies on laboratory animals

- Furuhashi et al (1983): nonteratogenic in rats (1g/kg e.v.), it has caused a bone delay but not malformations at 2g/kg e.v..

Cefriaxon – J01DA013

This is a cephalosporin of third generation. Patented in 1979.

Cohort retrospective studies with internal controls

- Rosa (1993), Michigan MSS: 60 exposures during the first trimester, 4 newborns with major defects, 3 expected: RR = 1.3 (IC 95%: 0.4-3.4).

Feto-neonatal effects: it's been used over the second half of pregnancy with no adverse effects in offspring (Cavenee et al 1993, Sanchez Ramos et al 1995).

Cefonicid – J01DA017

This is a cephalosporin of second generation. Patented in 1986.

We have been unable to locate references on possible human reproductive effects of this agent, or have we found any similar studies on laboratory animals.

Cefatrizina – J01DA21

This is a first generation cephalosporin. Patented in 1975.

We have been unable to locate references on possible human reproductive effects of this agent.

Studies on laboratory animals

- Matsuzaki et al (1976 a-b): nonteratogenic in rats and mice (3,200 mg/kg per os), but reduced neonatal weight; increased fetal death rate in rabbits (400-800 mg/kg per os).

Ceftizoxime – J01DA22

This is a third generation cephalosporin. Patented in 1977.

We have been unable to locate references on possible human reproductive effects of this agent.

Studies on laboratory animals

- Fukuhara et al (1981): nonteratogenic in rats (1,000 mg/kg/day)

Cefixime – J01DA23

This is a third generation cephalosporin. Patented in 1992.

Prospective cohort studies without controls

- Wilton et al (1998): 11 first trimester exposures: 7 healthy newborns, 2 miscarriages, 1 pregnancy termination and 1 unknown outcome.

Cefepime – J01DA24

This is a third generation cephalosporin. It is available in Italy since 1995.

We have been unable to locate references on possible human reproductive effects of this agent.

Studies on laboratory animals

- Kai et al (1973): nonteratogenic in rats (1,000 mg/kg).
- Hata et al (1992): nonteratogenic in rats (1 g/kg subcutaneous).
- Hattori et al (1992): nonteratogenic in rats (750 mg/kg per os).

Cefodizima – J01DA25

This is a third generation cephalosporin. It is available in Italy since 1993.

We have been unable to locate references on possible human reproductive effects of this agent.

Studies on laboratory animals

- Kitatani et al (1988): nonteratogenic in rats (3 g/kg e.v.), but reduced neonatal weight.

Cefradina – J01DA31

This is a first generation cephalosporin. Patented in 1969.

Retrospective cohort studies with internal controls

- Rosa (1993), Michigan MSS: of 339 first trimester exposures, 29 newborns with major defects, 14 expected: RR = 1.9 (CI 95%: 1.3-2.8). 9 observed congenital cardiopathies, 3 expected. RR= 3.0 (CI 95%: 1.4-5.7).
- Aselton et al (1985), Seattle GHC: none of the 54 newborns exposed in the first trimester had congenital anomalies.

Cefoperazone – J01DA32

This is a third generation cephalosporin. Patented in 1978.

We have been unable to locate references on possible human reproductive effects of this agent.

Studies on laboratory animals

- Tanioka and Koizumi (1979): nonteratogenic in monkeys (9 pregnancies) the dose being of 400 mg/kg e.v.
- Nakada et al (1980): nonteratogenic in rats (1 g/kg subcutaneous).

Cefopodoxime – J01DA33

This is a third generation cephalosporin. It is available in Italy since 1995.

We have been unable to locate references on possible human reproductive effects of this agent.

Studies on laboratory animals

- Tanase and Hirose (1988): nonteratogenic in rats (500 mg/kg per os).

Ceftexolo (ceftezolo) – J01DA36

This is a first generation cephalosporin. Patented in 1968.

We have been unable to locate references on possible human reproductive effects of this agent.

Ceftibuten – J01DA39

This is a third generation cephalosporin, considered the father of a sub-class of cefemic beta-lactam antibiotics: the carboxyethylidenic antibiotic. It is available in Italy since 1993.

We have been unable to locate references on possible human reproductive effects of this agent.

Studies on laboratory animals

- Hasegawa and Takegawa (1989): nonteratogenic in rats (4-g/kg gavage).
- Hasegawa and Fukiishi (1989): nonteratogenic in rabbits (40-mg/kg gavage).

Cefmetazolo – J01DA40

This is a second-generation cephalosporin. It is available in Italy since 1992.

We have been unable to locate references on possible human reproductive effects of this agent.

Studies on laboratory animals

- Masuda et al (1978): nonteratogenic in rats (1 g and 2 g/kg e.v.) and in mice (1 g/kg e.v.).
- Esaki et al (1980): nonteratogenic in beagle dog (1g/kg per os).

Cefprozil – J01DA41

This is a third generation cephalosporin. It is available in Italy since 1998.

We have been unable to locate references on possible human reproductive effects of this agent, or have we found any similar studies on laboratory animals.

J01DA class conclusions: Despite the widespread use of cephalosporin also during pregnancy we have not found a sufficient literature on the outcomes of their intake in the first trimester of gestation. Nonetheless, the studies done on first- and second-generation cephalosporin are sufficient to suggest that there is no evidence of increased human reproductive risk. Besides, the use of cephalosporin at various stages of pregnancy has not revealed any adverse effects on newborns. As a matter of fact, ADEC, FASS, and WGZ consider cefalexin and cefalotin drugs of choice in pregnancy. Third generation cephalosporins instead, having different pharmacokinetic properties, need to be still further tested. In case of inadvertent exposure an increase in the background reproductive risk is not likely, in consideration of their pharmacological class. There is a lack of reported anomalies over the long period of commercialization and studies carried out on laboratory animals have not shown teratogenic activity (records provided by manufacturer for registration, not available in databases). Rosa's assumption that there be an association of some cephalosporins with oral schisis and cardiopathies requires an in-depth study.

J01DF – Monobactams

Aztreonam – J01DF01

This is a monocyclic beta-lactam antibiotic. Patented in 1981.

We have been unable to locate references on possible human reproductive effects of this agent.

Studies on laboratory animals

- Furuhashi et al (1985 a,b,c): nonteratogenic in rats up to 750 mg/kg e.v.

Conclusions: There is no written evidence in literature of specific studies concerning the use of aztreonam in human pregnancy. In case of inadvertent exposure an increase in the population background reproductive risk is not likely, due to its pharmacological class. The lack of reported anomalies over the long period of commercialization and the absence of teratogenic activity on laboratory animals (records provided by manufacturer for registration, not available in databases) should be also considered.

J01E - Sulfonamides

These are sulfanilamide derivatives. They are antimicrobial agents with primarily broad-spectrum bacteriostatic effects. As structural analogs and competitive antagonists of para-aminobenzoic acid (PABA) they prevent bacteria from using PABA in the synthesis of folic acid. Such a mechanism is not active in mammalian cells. (Goodman and Gilman 1996).

Prospective cohort studies with internal controls

- Heinonen et al (1977), CPP: of 1,455 exposures to various sulphamides (as, for instance sulfamethazine, sulfanylacetamide, sulfapyridine and sulfamethoxazole) in the early 16 weeks, 92 newborns had congenital anomalies: ARR = 1.4 (CI 95%: 1.1-1.7).

Case-control studies, nonspecific

- Nelson and Forfar (1971): 458 newborns with congenital anomalies, 911 healthy controls. 17 newborns with congenital anomalies exposed in the first trimester to sulphamides vs. 27 among controls. OR = 1.3 (CI 95%: 0.7-2.4).

Case-control studies, specific

- Torfs et al (1996), California BDMP: 110 cases of gastroschisis, 220 healthy controls. AOR for first-trimester exposure = 0.4 (CI 95%: 0.1-3.4).

Feto-neonatal effects: The use of sulphamides prior to birth has been associated to hemolytic anemia (Heckel 1941, Ginzler and Cherner 1942, Perkins 1971) and probable hyperbilirubinemia, specially in premature infants (Heckel 1941, Ginzler and Cherner 1942, Lucey and Driscoll 1959, Kantor et al 1961, Dunn, 1964 and Perkins 1971). The occurring of kernicterus is theoretically possible, although it has never been reported.

Sulfadiazine – J01EC02

This is a sulphamide with intermediate action. Patented in 1946.

Cohort studies with internal controls

- Heinonen et al (1977), CPP: 95 exposed in the early 16 weeks, 3 newborns with congenital anomalies: ARR = 0.7 (CI 95%: 0.2-2.1).

Sulfamazone – J01ED09

This is a sulphamide with protracted action. It is available in Italy since 1966.

We have been unable to locate references on possible human reproductive effects of this agent, or have we found any similar studies on laboratory animals.

J01E class conclusions: We have been able to find a couple of rather exhaustive studies on the use of sulfonamides in the first trimester of human pregnancy showing that there is no risk increase as far as congenital anomalies. Nevertheless, while evaluating prospective prescription, a possible population-

based reproductive increase might be considered, based on recent studies carried out on sulfamethoxazole and on experimental teratogenicity in laboratory animals. Such studies show in fact the possibility of a connection with folic acid deficiency. These drugs should be given only in case of absolute need and always supplemented with folic acid. Their use at last stage of pregnancy may determine severe hyperbilirubinemia in the infant, and – theoretically, kernicterus.

J01EE – Association of sulfonamides with trimethoprim, and its derivatives

Sulfamethoxazole + trimethoprim (co-trimoxazole) – J01EE03

Sulfametrolo + trimethoprim – J01EE03

This is an association between diaminopyridine (trimethoprim) and a sulphamide (sulfamethoxazole) in the ratio of 1:5. Sulfamethoxazole prevents bacterial from producing folic acid while trimethoprim acts on bacterial dihydrofolate reductase as a further blocker of folic acid synthesis. The affinity of trimethoprim with bacterial dihydrofolate reductase is 10,000 times the affinity with human cells. It is therefore believed that human changed metabolism of folates, induced by trimethoprim, although little may cause megaloblastic anemia (Stebbins et al 1973) and increase homocysteine (Smulders et al 1999). Patented in 1959.

Case report

- Koutras and Fisher (1982): 1 newborn with Niikawa-Kuroki syndrome (mental retardation, reduced development, and characteristic facies) exposed in the second month of pregnancy.
- Rojansky et al (2002): 1 fetus with caudal regression (sacral-vertebral aplasia and renal agenesis) exposed in the first trimester of gestation to hair lotion composed of minoxidil and sulfamethoxazole + trimethoprim.

Controlled clinical studies for the assessment of the therapy

- Five studies have been carried out, four of which controlled to assess the drug's efficacy in pregnancy. Colley et al (1982), Bailey (1984) and Williams et al (1966) have surveyed three groups of respectively 89, 42 and 10 women during the first trimester. Coggiola (1973) and Bailey et al (1983) have instead surveyed two groups of 53 and 44 women throughout pregnancy. The sample group comprehended a few more than 200 women, and no increased malformation has been uncovered.

Case-control studies, nonspecific

- Czeizel (1990 and 2001), Hungarian CCSCA: 22,865 cases of infants with congenital anomalies. 38,151 healthy controls.

351 cases and 443 controls treated with co-trimoxazole (trimethoprim-sulfamethoxazole) have been checked:

- i. OR for exposures in the first month of pregnancy
 1. As per all defect, in general = 1.8 (IC 95%: 1.3-2.6)
 2. As per NTD = 4.3 (CI 95%: 2.1-8.6)
 3. As per cleft lip/palate = 3.0 (CI 95%: 1.4-6.5)
 4. As per renal impairments = 3.8 (CI 95%: 1.4-10.5)
 5. As per multiple defects = 2.9 (CI 95%: 1.4-6.1)
- ii. OR for exposure in the second and third month of pregnancy:
 1. As per congenital defects in general = 1.6 (CI 95%: 1.2-2.2)
 2. As per cardiovascular defects = 2.1 (CI 95%: 1.4-3.3)
 3. As per multiple defects = 2.2 (CI 95%: 1.1-4.4)

Cohort retrospective studies with internal controls

- Rosa (1993), Michigan MSS: of 2,296 first trimester exposures to co-trimoxazole, 126 newborns with major defects, 98 expected: RR = 1.3 (CI 95%: 1.1-1.5), more NTD and oral schisis than expected. Cardiovascular defects: 37 among exposures and 23 expected: RR = 1.6 (CI 95%: 1.1-2.2).

Case-control studies, specific

- Hernandez-Diaz et al (2000, 2001 a,b), Boston SEUBDS: Cases (infants or fetuses): 1,242 with NTD; 3,870 with cardiovascular defects; 1,962 with oral schisis; 1,100 with renal impairments. Controls: 8,387 (6,600 for the analysis on NTD) showing malformations possibly related to poor folic-acid activity. Surveyed exposures: dihydrofolate reductase inhibitors used in 2nd and 3rd month of gestation (1st and 2nd month as per NTD). Trimethoprim, triamterene and sulfalazine were among them, but quantities were not mentioned. AOR:
 - As per NTD = 4.8 (IC 95% 1.5-16.1);
 - As per cardiovascular defects = 3.4 (IC 95% 1.8-6.4);
 - As per cardiovascular defects, only if exposed to trimethoprim = 4.2 (IC 95% 1.5-11.5);
 - As per oral schisis = 2.6 (IC 95% 1.1-6.1);
 - Renal impairments have not been analyzed (number of exposures <5)

According to a sub-groups survey OR showed to be lower in women who had also taken supplementary folic acid.

Feto-neonatal effects: neonatal neutropenia (Bruel et al 1999).

Conclusions: Available studies on first trimester exposures to co-trimoxazole and trimethoprim do confirm the hypothesis raised long ago (McEwen 1971, Smithells 1983). There appears to be an increased reproductive risk particularly for cardiovascular defects (more frequent and therefore further studied), but the increase is also relevant to other malformations currently reckoned to be associated with folates metabolism (NTD, cleft lip/palate and urinary anomalies). Increased risk magnitude can be tentatively calculated around 2-4 times the population of reference. Here are the issues suggesting causative effects: timing, biologic plausibility, concordance of opinions among different researchers, risk specificity, risk magnitude and control of confounding factors (in some studies). Trimethoprim appears teratogenic in some studies on rats (Helm et al 1976, NIEHS 1998), but teratogenic outcomes are not averted by contemporaneous administration of folic acid. This fact suggests a complex activity, not directly linked to inhibition of folates synthesis. Teratogenic effects of NTD on mice are strengthened by contemporaneous administration of valproic acid and this is the reason why such an association should be avoided during human pregnancy (Elzamar and Nau 1993).

J01FA – Macrolides

These drugs have been marketed for a long time and they are widespread all over the world. They are made of a lactam ring to which various sugars are attached. They inhibit bacterial synthesis blocking translocation processes. They have a bacteriostatic activity.

Erythromycin – D010AF02 – J01FA01 – S01AA17

It is a natural antibiotic (*Streptomyces erythreus*). Marketed as estolate, stearate and ethylsuccinate. It barely crosses the placenta (Kiefer et al 1955, Philipson et al 1973). Patented in 1952.

Case report

- Jaffe et al (1975): 1 newborn exposed in the first trimester missing the left tibia (contemporaneous exposure to other drugs).

Case-control studies, nonspecific

- Czeizel et al (1999), Hungarian CCSCA: 22,865 newborns with congenital anomalies, 38,151 healthy controls. 113 of the cases and 172 of the controls were exposed to erythromycin. OR = 1.1 (CI 95%: 0.6-3.5).

Retrospective cohort studies with internal controls

- Aselton et al (1985), Seattle GHC: 260 first trimester exposures. Six newborns with congenital anomalies (2.3%) not specified by the authors. OR = 1.5 (CI 95%: 0.6-3.5).
- Rosa (1993), Michigan MSS: 6,972 first trimester exposures, 320 newborns with major defects, 297 expected: RR = 1.1 (CI 95%: 0.9-1.3). There was no increase in malformations among the 6 analyzed groups of malformations, including cardiopathies (77 cases).

Prospective cohort studies with internal controls

- Heinonen et al (1977), CPP: 79 exposed during the early 16 weeks, 5 newborns with congenital anomalies: ARR = 1.4 (CI 95%: 0.6-3.3).

Nested case-control studies, specific in the prospective cohort of all newborns

- Kallen and Otterblad Olausson (2003), Swedish MBR: Cases: 5,015 newborns with cardiovascular defects, 27 of which exposed to erythromycin in the first trimester; 577,730 controls, 1,588 of whom exposed. OR for CVS defects = 1.9 (CI 95%: 1.3-2.8).

Feto-neonatal effects: Erythromycin estolate may cause hepato-toxicity during pregnancy (McCormack et al 1977). The treatment of newborns with erythromycin in the first two weeks of life may cause hypertrophic stenosis of pylorus (MMWR 1999, Honein et al 2000, Hauben and Amsden 2002) mainly in female infants with estimated OR = 10.3 (CI 95%: 1.2-92.3) (Sorensen 2003). Such an issue had already been considered some years ago (1976) by doctor Sanfilippo, an attentive surgeon and pediatrician. The risk for pyloric stenosis is about 8-10 times higher in male than in female infants (Cooper et al 2002, Sorensen et al 2003). Exposure throughout pregnancy or during just the last weeks does not increase the risk for pyloric stenosis (cooper et al 2002, Louik et al 2002). Erythromycin has been used in the third trimester, with no adverse effects on fetus/newborn, in order to reduce SBEA colonization (Menerstein et al 1980, Easmon et al 1983) and in the treatment of genital mycoplasma (Quinn et al 1983, Kass and Mc Cormack 1984).

Conclusions: Available studies concerning first-trimester exposure to erythromycin do not show an increased reproductive risk. No adverse effects have been noticed on newborns when the drug has been used at other stages of pregnancy. In particular, pyloric stenosis is not increased when the infant is exposed in the early two weeks of life. It would be useful to evaluate the hypothesis brought up by a Swedish study about an association of the drug with cardiovascular defects. ADEC considers erythromycin a drug of choice.

Spiramycin – J01FA02

This natural antibiotic (*Streptomyces ambofacies*) crosses the placenta and its concentration is 2-4 times the maternal serum. It is available in Italy since 1985.

Case-control studies, nonspecific

- Czeizel et al (1999), Hungarian CCSCA: 22,865 newborns with congenital anomalies, 38,151 healthy controls. OR for exposure to spiramycin = 1.4 (CI 95%: 0.7-3.1).

Feto-neonatal effects: spiramycin is regularly used in the treatment of toxoplasmosis in pregnancy, with no adverse outcomes on fetus/newborns (Desmots and Couvreur 1984, Daffos et al 1988, Hohlfeld 1989, Szenasi et al 1997, Vergani et al 1998, Foulon et al 1999, Bessieres et al 2001, Wallon et al 2002, Gratz et al 2002, Greco et al 2003).

Midecamycin – J01FA03

It is a natural antibiotic (*Streptomyces mycarofaciens*). [Here is REPROTOX description: Midecamycin refers to a macrolide antibiotic complex derived from *Streptomyces mycarofaciens*].

It is available in Italy since 1984.

We have been unable to locate references on possible human reproductive effects of this agent, or have we found any similar studies on laboratory animals.

Roxithromycin – J01FA06

It is a semisynthetic antibiotic derived from erythromycin. It is available in Italy since 1989.

Case-control studies, nonspecific

- Czeizel et al (1999), Hungarian CCSCA: 22,865 newborns with congenital anomalies, 38,151 healthy controls. OR for exposure to roxithromycin = 0.9 (CI 95%: 0.4-2.1).

Josamycin – J01FA07

It is a natural antibiotic derived from *Streptomyces narbonensis-josamyceticus*. Patented in 1975.

Case-control studies, nonspecific

- Czeizel et al (1999), Hungarian CCSCA: 22,865 newborns with congenital anomalies, 38,151 healthy controls. OR for exposure to josamycin = 3.3 (CI 95%: 0.7-15.7).

Feto-neonatal effects: josamycin is regularly used in the treatment of toxoplasmosis in pregnancy, with no adverse outcomes on fetus/newborns (Monzonis and Perales 1983, Camarasa and Monfort 1984).

Troleandomycin – J01FA08

It is available in Italy since 1974.

Prospective cohort studies with internal controls

- Heinonen et al (1977), CPP: 4 healthy newborns exposed in the early 16 weeks of pregnancy.

Clarithromycin – J01FA09

It is a semisynthetic antibiotic derived from erythromycin. It is available in Italy since 1990.

Cohort studies, without control

- Schick (1996): 34 healthy newborns exposed in the first trimester.

Retrospective cohort studies with external controls

- Drinkard et al (2000): of 149 exposures in the first trimester, 5 newborns had major defects, 3 had minor defects, 4 infants had retained testis. Incidence of major defects = 3.4% (CI 95%: 0.5-6.3%) with a confidence interval ranging within the usual rate of 2-3%.

Prospective cohort studies with internal controls

- Einarson et al (1998), 5 TIS (one of which Italian): 122 first trimester exposures, as many controls. RR as per exposure to clarithromycin in the first trimester for major defects = 1.5 (CI 95%: 0.3-8.8), for minor defects = 1.1 (CI 95%: 0.4-3.4)

Feto-neonatal effects: no adverse outcomes in the 2 newborns exposed in the second half of pregnancy for maternal Q fever (Jover-Diaz 2001, Hellmeyer et al 2002).

Azithromycin – J01FA10

It is a macrolide antibiotic belonging to the new class of Azalides, derived from erythromycin. Patented in 1961.

Prospective cohort studies without controls

- Wilton et al (1996): 12 first trimester exposures, 1 ectopic pregnancy, 1 VIP, 10 healthy newborns.

Feto-neonatal effects: there were no adverse outcomes in mothers and newborns exposed after the first trimester of pregnancy (Bush and Rosa 1994, Adair et al 1998, Choi and Pai 1998, Ramsey et al 2003).

Miocomycin – J01FA11

It is a semisynthetic antibiotic derived from midecamycin. It is available in Italy since 1984.

We have been unable to locate references on possible human reproductive effects of this agent.

Studies on laboratory animals

- Moriguchi et al (1984): nonteratogenic in rats and rabbits

Rokitamycin J01FA12

It is another semisynthetic antibiotic derived from midecamycin. It is available in Italy since 1992.

We have been unable to locate references on possible human reproductive effects of this agent, or have we found any similar studies on laboratory animals.

Flurithromycin – J01FA14

It is available in Italy since 1997.

We have been unable to locate references on possible human reproductive effects of this agent, or have we found any similar studies on laboratory animals.

J01FA class conclusions: Some of the agents in this group of drugs have been thoroughly studied, particularly erythromycin, but others have not and the available data on their employment in human pregnancy are limited. In case of inadvertent exposure an increase in the population-based risk is not likely, due to

scarce surveys, to the lack of reported anomalies over the long period of commercialization and the lack of teratogenic effects on laboratory animals. (Records provided by manufacturer for registration, not available in databases). The hypothesis raised by Kallen and Otterblad Olausson (2003), concerning an increased specific risk of cardiopathies deserves further evaluation.

J01FF – Lincosamides

These are antibiotics, aminoglycosides analogs.

Clindamycin – G01AA10 – J01FF01

It is a semisynthetic aminoglycoside, derived from lincomycin. Patented in 1968.

Retrospective cohort studies with internal controls

- Rosa (1993), Michigan MSS: of 647 first trimester exposures, 31 newborns with major defects, 28 expected: RR = 1.1 (CI 95%: 0.7-1.6).

Feto-neonatal effects: there are no adverse effects in 2nd and 3rd-trimester exposures (McCormack et al 1987). A significant reduction in the incidence of preterm births has been noticed as for women showing nonspecific vaginitis treated with cream clindamycin during the second trimester (Lamont et al 2003).

Lincomycin – J01FF02

It is a natural aminoglycoside (*Streptomyces lincolnensis*) that in the umbilical cord reaches a concentration as high as 25% the quantity in maternal serum. Patented in 1963.

Prospective cohort studies with internal controls

- Heinonen et al (1977), CPP: 1 healthy newborn exposed in the early 16 weeks.
- Mickal and Panzer (1975): 302 newborns exposed at various stages of pregnancy and followed over different periods of time since birth, some up to 7 years. No increase in malformations or changes in psychomotor and physical development were noticed compared to a control group.

Feto-neonatal effects: no adverse effects in exposures at various stages of pregnancy (Mickal and Panzer 1975).

J01FF class conclusions: Both available studies taken in consideration fail to report an increased risk in congenital anomalies. In case of exposure such a risk is not likely, due to the analogy with other aminoglycosides, the lack of reported anomalies over the long period of commercialization and the absence of teratogenic effects on laboratory animals. (Records provided by manufacturer for registration, not available in databases). ADEC and WGZ consider these agents drugs of choice in pregnancy.

J01G – Aminoglycosides

Case-control studies, nonspecific

- Czeizel et al (2000), Hungarian CCSCA: 22,865 newborns with congenital anomalies. 38,151 healthy newborns. OR for exposure to aminoglycosides (gentamycin, streptomycin, tobramycin via parenteral route and neomycin orally) = 1.5 (CI 95%: 0.9-2.4).

J01GA – Streptomycins

Streptomycin – J01GA01

It is a natural aminoglycoside (*Streptomyces griseus*). Patented in 1948.

Medical reports and small cohort studies without controls

- Watson and Stow (1948), Leroux (1950), Bolletti and Croatto (1958), Rebattu et al (1960), Kern (1962), Varpela and Hietalahti (1965) Varpela (1969), Khanna and Bhatia (1969), Shardein (1976), Warkany (1979), Snider et al (1980), Donald and Sellars (1981) and Donald et al (1991). They have all described single cases exposed to streptomycin showing hearing problems of various types. Small groups of women exposed to streptomycin and didrostreptomycin have also been surveyed.

Cohort studies without controls

- Conway and Birt (1965), Matsushima (1967) Rasmussen (1969): 177 exposures to streptomycin or didrostreptomycin, 11 light auditory impairments
- Varpela et al (1969): of 50 exposures to streptomycin or didrostreptomycin, two children had auditory defects
- Ganguin and Rempt (1970): 44 exposures to streptomycin, didrostreptomycin and isoniazide. 5 newborns with hearing anomalies. About 10% first trimester exposures may show severe impairments of the eighth cranial nerve

Studies on cases without controls

- Robinson and Cambon (1964): of 300 infants showing impairments of the auditory function, only 2 had been exposed to streptomycin

Case-control studies, nonspecific

- Czeizel et al (2000), Hungarian CCSCA: 22,865 newborns with congenital anomalies. 38,151 healthy newborns. OR for exposures to streptomycin = 0.5 (CI 95%: 0.2-3.9). There are no studies regarding outcomes on hearing.

Prospective cohort studies with internal controls

- Heinonen et al (1977), CPP: 135 exposures in the early 16 weeks, 5 newborns with congenital defects: ARR = 0.8 (CI 95%: 0.4-1.9). There are no studies regarding outcomes on hearing.

Conclusions: Leroux (1950) was the first to report an association between prenatal exposure to streptomycin (1 g/day in the last month of pregnancy) and deafness. 60 more cases were reported since then (including 8 cases of exposure to diidrostreptomycin and 10 to kanamycin). The risk assessment of oto-vestibular impairments following prenatal exposure to aminoglycosides is about 8-10% (Ganguin and Rempt 1970, Schardein 2000). Auditory damage due to streptomycin or diidrostreptomycin is unsteady: light anomalies are mostly uncovered that can be detected through specialized tools. Vestibular impairment alone may sometimes occur and the last trimester of pregnancy is mostly liable to changes. Evidence of a causative relationship between exposure to aminoglycosides and oto-vestibular impairment is also given by the side effect of these antibiotics provoke postnatally and in adults. There is no evidence for streptomycin or diidrostreptomycin to cause other congenital defects besides auditory damage.

J01GB – More aminoglycosides

Tobramycin – J01GB01

This natural aminoglycoside (*Streptomyces tenebrarius*) reaches the same concentration rate in fetal tissues as in maternal organs. Patented in 1972.

Retrospective cohort studies with internal controls

- Rosa (1993), Michigan MSS: of 81 first trimester exposures, 3 newborns had major defects, 3 expected: RR = 1.0 (CI 95%: 0.2-2.9).

Case-control studies, nonspecific

- Czeizel et al (2000), Hungarian CCSCA: 22,865 newborns with congenital anomalies. 38,151 healthy newborns. OR for exposure to tobramycin = 0.8 (CI 95%: 0.2-3.9).

Gentamycin – J01GB03 – D06AX07 – S01AA11

This is a natural aminoglycoside (*Micromonospora purpurea*). Patented in 1963.

Case report

- Hulton and Kaplan (1955): 1 newborn exposed to gentamycin and prednisolone at 7th-8th week, who at 4 and a half years of age showed cystic renal dysplasia.

Medical trials

- Wing et al (1998): no congenital anomalies or other side effects were noticed in 57 infants exposed to evaluation trial of therapy efficiency.

Case-control studies, nonspecific

- Czeizel et al (2000), Hungarian CCSCA: 22,865 newborns with congenital anomalies. 38,151 healthy newborns OR for exposure to gentamycin = 1.7 (CI 95%: 0.9-3.2).

Amikacin – J01GB06

It is a semisynthetic aminoglycoside derived from Butirosine and produced from *Bacillus Circulans*. Patented in 1972.

We have been unable to locate references on possible human reproductive effects of this agent.

Studies on laboratory animals

- Matsuzaki et al (1975 a-b): nonteratogenic in rats and mice at 2-27 times human therapeutic doses.
- Akutsu et al (1982): nonteratogenic in rats (200 mg/kg intraperitoneal).

Metilmicin – J01GB07

It is a semisynthetic aminoglycoside derived from sisomycin and chemically related to gentamycin. Patented in 1974.

We have been unable to locate references on possible human reproductive effects of this agent.

Studies on laboratory animals

- Bamonte et al (1979), Weinberg et al (1981): nonteratogenic in rats and rabbits at 5-20 times human therapeutic doses.
- Nomura et al (1982), Furuashi et al (1982): nonteratogenic in rats and rabbits (100-mg/kg i.m.).

J01GB class conclusions: There are few studies in literature relevant to just some of the drugs included in this therapeutic class (gentamycin and tobramycin) which have not shown teratogenic effects. Nonetheless, chemical-pharmacological characteristics should be considered, as well as similarities with other aminoglycoside antibiotics and their teratogenicity on hearing and renal function in laboratory animals. All drugs in this group appear to have a potentially nephrotoxic and/or ototoxic activity. Nevertheless their use in pregnancy in case of severe infections is recommended.

(documents provided by manufacturer for registration, not available in data bases).

M03BX – More muscle relaxants having a central activity

Baclofen – M03BX01

This is a derivative of gamma-aminobutyric acid. Patented in 1969.

We have been unable to locate references on possible human reproductive effects of this agent.

Case reports

- Delhaas and Verhagen (1992), Munoz et al (2000): 3 healthy newborns exposed per intrathecal way throughout pregnancy.
- Ratnaayaka et al (2001): 1 healthy newborn exposed throughout pregnancy, having neonatal convulsions (in 7 days) due to drug suspension.

Studies on laboratory animals

- Hirooka (1976 a-b) Hirooka et al (1976): no teratogenic outcomes were uncovered in mice (15mg/kg per os), rats (12.5 mg/kg per os) and rabbits (4.55 mg/kg per os).

Tizanidine – M03BX02

This is a derivative of imidazoline. It is available in Italy since 1993.

We have been unable to locate references on possible human reproductive effects of this agent.

Studies on laboratory animals

- Nakajima et al (1985): minimal skeletal anomalies in rats treated with 3-10 mg/kg/day.

Pridinol – M03BX03

Patented in 1941.

We have been unable to locate references on possible human reproductive effects of this agent, or have we found any similar studies on laboratory animals.

Tiocolchicoside – M03BX05

J01MA – Fluoroquinolones

Prospective cohort studies without controls

- Schaefer et al (1966), report 2 cohort groups. (a) ENTIS: 394 exposures (mostly to norfloxacin) in the first trimester, 23 congenital anomalies, 11 of which showing major defects not associated with chromosomal anomalies (2.8%). See single drugs for specifications. And (b) manufacturer: 4 congenital anomalies out of 63 first trimester exposures (6.3%): 2 hypospadias, 1 cerebellar hypoplasia and 1 right-forearm agenesis.
- Santolaria et al (1998), TIS Surveillance Pharmacological Center in Lyon: of 106 first-trimester exposures, 3 had major defects: anencephaly (norfloxacin), bilateral vesicouretral reflux with hydronephrosis (norfloxacin)

and hypospadias (ofloxacin). 3 more had light or doubtful congenital anomalies: minimal ventricular defect (norfloxacin), bilateral talipes valgus (pefloxacin), and cardiac murmur (norfloxacin). Major congenital anomalies incidence: 3/105 (2.8%).

Prospective cohort studies with internal controls

- Berkovitch et al (1994), TIS Motherisk Program: 31 live births exposed to quinolones (norfloxacin and ciprofloxacin), 30 controls. Exposures mostly occurred at 6 weeks of gestation. None of the exposed infants had congenital anomalies, 1 of the controls had a defect of the interventricular septum of heart. RR = 0.0 (CI 95%: 0.0-17.8). No anomalies were observed during the follow up until 34 months of age.
- Loebstein et al (1998) and Andreou et al (1995), a broadening of the study by Berkovitch, 4TIS (1 In Canada, 2 in the US and 1 in Italy): 133 newborns exposed to fluoroquinolones (about half of them to norfloxacin) between 4th and 13th week of gestation, and controls (similar as per main variables). 188 newborns exposed to antibiotics considered nonteratogenic. 3 newborns with congenital anomalies (2 IVD and 1 PDA) vs. 5 among controls (2 IVD, 1 DIA, 1 hypospadias and 1 subluxation of the hip). RR = 0.9 (CI 95%: 0.2-3.5). Psychomotor development tested with Denver was normal until beyond one year of age. This study had the opportunity to identify an RR of 3.5 or over, for general malformations (incidence basic date of 3%).
- Larsen et al (2001), PEP Database North Jutland: 57 exposures to fluoroquinolones, 17,259 controls. RR for first trimester exposure = 1.3 (CI 95%: 0.3-5.3).

Ofloxacin – J01MA01

This is a third-generation quinolone. It is available in Italy since 1987.

Case report

- Peled et al (1991): 1 healthy newborn exposed at week 19 of gestation to 400 mg/day of ofloxacin for 6 days.

Prospective cohort studies without controls

- Wilton et al (1996): 8 healthy newborns exposed in the first trimester.
- Schaefer et al (1996), ENTIS: 61 live births 7 of which (11.5%) showing congenital defects (myelomeningocele, urethral stricture, chriptorchism, hypospadias, inguinal hernia, bilateral hip dysplasia and defect of interatrial septum of heart).

Ciprofloxacin – J01MA02

This is a second-generation quinolone, fluoroquinolone. It is available in Italy since 1987.

Case report

- Thorsteinsson and Bergman (1989): 1 healthy newborn (follow up until 16 months of age) exposed for 5 days at 3rd-4th weeks.
- Baroncini et al (1996): 5 healthy newborns exposed in the first trimester

Retrospective cohort studies without controls

- Schluter (1989) and Bomford et al (1993): exposures reported to the manufacturer: 52 healthy newborns exposed in the first trimester, 11 healthy newborns exposed after the first trimester, 8 newborns with various different types of defects, 18 VIP, 10 miscarriages, 4 fetal deaths.

Retrospective cohort studies with internal controls

- Rosa (1993), Michigan MSS: 132 first trimester exposures, 3 newborns with major defects, 6 expected. RR = 0.5 (CI 95%: 0.1-1.5).

Prospective cohort studies without controls

- Wilton et al (1996): 5 healthy newborns in the first trimester
- Schaefer et al (1996), ENTIS: 71 first trimester exposures, 50 live births, and 3 of whom showing congenital anomalies (angioma, dysplasia of the hip, trisomy). 6 out of 116 exposures to ciprofloxacin prospectively gathered by the manufacturer had congenital anomalies (hypospadias, dysplasia of the hip, CNS defect, and hypospadias with bilateral inguinal hernia, acaridae and forearm amputation).

Feto-neonatal effects: used after the first trimester in the treatment of Q fever (Ludlam et al 1997), of typhoid fever Leung et al 1995, Koul et al 1995), and of bacillary dysentery (*Schigella dysenteriae*) (Laureillard et al (1989), with no adverse effects on mother and infant.

Pefloxacin – J01MA03

This is a second-generation quinolone, fluoroquinolone. It is available in Italy since 1988.

Prospective cohort studies without controls

- Schaefer et al (1996) ENTIS: 57 first trimester exposures, 43 live births 2 of whom showing congenital anomalies (4.7%) (phenylketonuria, pulmonary cardiopathy). 5 more healthy newborns exposed also to norfloxacin.

Enoxacin – J01MAA04

This is a second-generation quinolone, fluoroquinolone. It is available in Italy since 1988.

Cohort prospective studies without controls

- Schaefer et al (1996) ENTIS: 1 healthy newborn exposed in the first trimester
- Wilton et al (1996): 1 healthy newborn exposed in the first trimester

Norfloxacin – J01MA06

This is a second-generation quinolone, fluoroquinolone, derived from nalidixic and pipemidic acids. Patented in 1979.

Prospective cohort studies without controls

- Schaefer et al (1996) ENTIS: 5 healthy newborns exposed in the first trimester
- Wilton et al (1996): 8 healthy newborns exposed in the first trimester

Retrospective cohort studies with internal controls

- Rosa (1993) Michigan MSS: 79 first trimester exposures, 5 newborns with major defects, 3 expected: RR = 1.7 (CI 95%: 0.5-3.9).

Lomefloxacin – J01MA07

This is a third generation, long-acting quinolone. It is available in Italy since 1992.

We have been unable to locate references on possible human reproductive effects of this agent.

Studies on laboratory animals

- Thesh et al (1988): nonteratogenic in rats (300 mg/kg/day).

- Umemura et al (1988): nonteratogenic in rabbits (100 mg/kg/day).

Rufloxacin – J01MA01

This is a third generation, long-acting quinolone. It is available in Italy since 1992.

We have been unable to locate references on possible human reproductive effects of this agent, or have we found any similar studies on laboratory animals.

Levofloxacin – J01MA12

This is a third-generation quinolone. It is available in Italy since 1998.

We have been unable to locate references on possible human reproductive effects of this agent.

Studies on laboratory animals

- Tesh et al (1998): nonteratogenic in rats (300 mg/kg/gavage)

Moxifloxacin – J01MA14

This is a third-generation quinolone. It is available in Italy since 2000.

We have been unable to locate references on possible human reproductive effects of this agent, or have we found any similar studies on laboratory animals.

J01MA class conclusions: The use of some quinolones in pregnancy cannot be associated with an increased reproductive risk, and others have not been specifically studied. The principle of pharmacological analogy is therefore to be used. Studies on laboratory animals have revealed the possibility of damages to articular cartilage in puppies (Linseman et al 1995) and caused by some quinolones. Such an event has not been observed in a small group of treated children (Danisovicova et al 1994). Arthralgia and tendinitis are side effects well known in adults (Schact et al 1989).

J01MB – More quinolones

Nalidixic acid – J01MB02

This is a first generation quinolone derived from naftiridine. Patented in 1961.

Case report

- Sogard-Andersen and Alsner (1967): 1 healthy newborn exposed in the first month of pregnancy
- Based on a study by Deonna and Guignard (1974) who reported 2 children with intracranial hypertension following the use of nalidixic acid, Asscher (1977) reviewed IVU treatment. He affirms that "nalidixic acid should not be prescribed in the second half of pregnancy since it may cause hydrocephaly also at low doses".

Retrospective cohort studies without controls

- Murray (1981): 6 healthy newborns exposed in the first trimester, 55 exposed in the second and third trimester, 1 newborn exposed in the third trimester with severe cardiac defect. No cases of intracranial hypertension or hydrocephaly.

Case-control studies, nonspecific

- Czeizel et al (2001) Hungarian CCSCA: 22,865 newborns with congenital anomalies 242 of which exposed, 38,151 healthy newborns, 377 of which

exposed. OR = 1.1 (CI 95%: 0.9-1.3). 7 cases of pyloric stenosis exposed in the late months of pregnancy. OR = 11.0 (CI 95%: 1.3-91.4). The association is only a stimulating hypothesis, whereas an association with hydrocephaly is not confirmed.

Prospective cohort studies with internal controls

- Heinonen et al (1977), CPP: 1 healthy newborn exposed during the early 16 weeks of gestation.

Feto-neonatal effects: no adverse outcomes have been reported on fetuses/newborns exposed after the first trimester (Barlow 1963, Gordon-Smart and Heughan 1965, Miller 1968, Mosiman 1975, Martin 1976). One single newborn with hemolytic anemia had been exposed in the second half of pregnancy (Belton and Jones 1965).

Conclusions: The available, limited studies we have found in literature do not show any association between nadilixic acid and a population-based reproductive risk increase. In case of exposure, then, such a risk is not likely due to a lack of reported anomalies over the long period of commercialization and considering the absence of teratogenic activity on laboratory animals (records provided by manufacturer for registration, not available in databases). In consideration of children intracranial hypertension mentioned in some case reports, the use of this drug is not recommended in the last trimester of pregnancy. The hypothesis of an association with hypertrophic stenosis should be further checked.

Piromidic acid – J01MB03

This is a first generation quinolone. Patented in 1972.

We have been unable to locate references on possible human reproductive effects of this agent, or have we found any similar studies on laboratory animals.

Pipemidic acid – J01MB04

This is a second-generation quinolone. Its concentration in umbilical cord and amniotic liquid is 40/80 % the amount found in maternal serum (Takase et al 1975). Patented in 1972.

We have been unable to locate references on possible human reproductive effects of this agent.

Studies on laboratory animals

- Nishimura et al (1976): it is nonteratogenic in rats (3,200-mg/kg gavage) but ureters and renal pelvis suffered a dilatation.

Cinoxacin – J01MB06

This is a second-generation quinolone. It is available in Italy since 1985

Prospective cohort studies with external controls

- Schaefer et al (1996), ENTIS: 2 healthy newborns were exposed in the first trimester.

Studies on laboratory animals

- Sato et al (1980), Sato and Kobayashi: nonteratogenic in rats (200 mg/kg/day 17-21st day) and in rabbits (800 mg/kg over the organogenetic period).

J01MB class conclusions: No specific studies are available in literature concerning the use in human pregnancy of agents belonging to this therapeutic class, except for nalidixic acid (See). In case of general exposure to quinolones a

population-based reproductive risk increase is not likely, due to a lack of reported anomalies over the long period of commercialization. Besides, teratogenic activity in laboratory animals has not been uncovered (records provided by manufacturer for registration, not available in databases).

J01XA – Glycopeptide antibacterial agents

Teicoplanin – J01XA02

This is a natural glycopeptide antibiotic (*Actinoplanes teichomyceticus*). It is available in Italy since 1989.

We have been unable to locate references on possible human reproductive effects of this agent, or have we found any similar studies on laboratory animals.

Conclusions: Specific studies concerning the use of teicoplanin in human pregnancy are not available in literature. In case of inadvertent exposure the following should be considered: a lack of reported anomalies over the period of commercialization and the absence of teratogenic activity in laboratory animals (records provided by manufacturer, not available in databases).

J01XB – Polymyxins

Colistin – J01XB01

It is available in Italy since 1985.

We have been unable to locate references on possible human reproductive effects of this agent.

Studies on laboratory animals

- Tomizawa and Kamada (1973): nonteratogenic per intraperitoneal injection in rats (50 mg/kg) and mice (150 mg/kg).
- Saitoh et al (1981): nonteratogenic in mice (500-mg/kg i.m.).
- Tsuijtan et al (1981): nonteratogenic in rats (25 mg/kg) and rabbits.

Conclusions: There are no specific available studies in literature concerning the use of colistin in human pregnancy. Just the following should be considered: the lack of reported anomalies over the period of commercialization and the absence of teratogenic activity in laboratory animals (records provided by manufacturer, not available in databases).

J01XD – Imidazole derivatives

Metronidazole – J01DX01 – A01AB17 – D06BX01 – G01AF01- P01AB01

This is a nitro-imidazole derivative, mainly used per vaginal way in protozoal vaginitis (i.e.: trichomonas) and in anaerobic-bacterial vaginitis. Patented in 1960.

Systematic review

- Burtin et al (1995): 7 cohort studies concerning first-trimester exposures comprehending 6 prospective studies for 253 pregnancy in all (Scott-Gray 1964, Robinson and Mirchandani 1965, Rodin and Hass 1966, Peterson et al 1966, Heinonen et al 1977, Morgan 1978) and 1 retrospective study on 1,083 pregnancies (Rosa et al 1987). OR has been assessed for congenital anomalies associated with first-trimester exposure vs. 2nd/3rd-trimester exposure, therefore with control as per the original disease. Cumulative OR in 7 studies = 0.9 (CI 95%: 0.7-1.2), OR in the 6 prospective studies = 1.0 (CI 95%: 0.5-2.2).

- Caro-Paton et al (1997): 5 studies in total. 4 cohort studies (Heinonen 1977, Morgan 1979, Rosa 1987 and Piper 1993) surveyed an overall of about 2,500 exposures, and 1 case-control study carried out by the Spanish cooperative registry for birth defects ECEMC. The study, not published, concerned 21,054 newborns with malformations. Seven studies were not included due to the lack of an adequate control group (Scott-Gray 1964, Robinson and Mirchandani 1965, Rodin and Hass 1966, Sands et al 1966, Peterson et al 1966, Beard et al 1979, and Aselton et al 1985). There were homogeneous results in the five studies where OR was examined globally, for congenital defects in first-trimester exposed infants, vs. non-exposed = 1.1 (CI 95%: 0.9-1.3). Despite some differences in the definition and choice of the published surveys, both meta-analyses give a pretty similar risk assessment. Besides, the use of this drug in pregnancy has been reported in small cohort studies relevant to about 250 more first-trimester exposures. There is no evidence of teratogenic outcomes associated with the use of the drug (Gray 1961, Robinson and Johnston 1961, Luthra and Boyd 1962, Schram and Kleinman 1962, Monroe 1963, Lyon et al 1963, Perl and Ragazzoni 1963, Andrews and Andrews 1963, Whitelaw et al 1963, Zacharias et al 1963, Kotcher et al 1964, Magnin et al 1966, Berget and Weber 1972, Culbertson 1974, Wallenburg et al 1975, Cantu e Garcia-Cruz 1982, Royer 1983, Mitchell and Teare 1984, Greenberg 1985, and Martinez et al 1992).

THE FOLLOWING STUDIES WERE NOT INCLUDED IN SYSTEMATIC REVIEWS

Case-control studies, nonspecific

- Czeizel and Rockenbauer (1998), Hungarian CCSCA: Cases = 17,300 newborns with congenital anomalies, 655 of which were exposed; controls = 30,663 healthy newborns, 1,041 of which were exposed. OR = 1.1 (CI 95%: 1.0-1.3). 9 cases of cleft lip +/- palate, with an OR = 8.5 (CI 95%: 1.1-68.9). This result should be taken as a vague working hypothesis, due to the possible memory and interview bias.

Retrospective cohort studies with internal controls

- Rosa (1993), Michigan MSS: 2,445 first trimester exposures, 100 newborns with congenital anomalies, 97 expected. RR = 1.0 (CI 95%: 0.8-1.3)
- Sorensen et al (1999) PEP Database North Jutland: 124 exposures with 2 defects (TGV and hypertelorism), 13,327 controls (5.2% with defects): OR = 0.4 (CI 95%: 0.1-1.8).

Prospective cohort studies with internal controls

- Diav-Citrin et al (2001), TIS Israel: 192 first trimester exposures, 597 controls. RR = 1.3 (CI 95%: 0.5-3.5).

STUDIES ON CARCINOGENICITY

Metronidazole has shown carcinogenicity in rodents, and Ames test for mutagenicity has been positive in mice and rats (Rustia and Shubik 1972, Anonymous 1975, Legator et al 1975, Rosenkranz and Speck 1975, Speck et al 1976, Rosenkranz et al 1976, Connor et al 1977, Rustia e Shubik 1979, Morgan 1979, Dobias 1980, Goldman 1980, Ewan et al 1980, Finegold 1980, Mirer e Silverstein 1980, Muller 1981, Roe 1983). Several studies on this possible outcome have been therefore carried out. Some studies relevant to mammals and human lymphocytes, both in vitro and in vivo, have not shown genotoxicity (Hartley-Asp 1979, Lambert et al 1979). No effects on humans have been noticed in two case-control studies (Beard et al 1979 and 1998, Friedman 1980) that were carried on for about 11- 19 years to assess possible carcinogenic and mutagenic outcomes. These cannot be considered final results, as far as – according to some researchers (Mirer and Silverstein 1980) – a longer period is necessary to assess the

carcinogenicity of a chemical agent in humans. Another study to check the possible association between infant tumors and exposure to metronidazole gave a negative result (Thapa et al 1998). Carvajal et al (1955) report one newborn exposed at 12th-13th week having a suprarenal neuroblastoma with hepatic metastases.

Conclusions: All extensive studies carried out on first-trimester exposures to metronidazole mainly regard its administration per vaginal way and do not show a population-based reproductive risk-increase. Nor its use over other periods of pregnancy has revealed any adverse effects on newborns. There is no convincing evidence to support the idea of tumor risk, although it cannot be completely dispelled. The hypothesis of routine use of the drug to decrease preterm birth (Morales et al 1994) has not been confirmed by further studies (Sonersen et al 1998, Carey et al 2000, Klebanoff et al 2001, Andrews et al 2003). Although not supported by other studies, Czeizel comment should be taken in consideration in further surveys relevant to this issue.

J01XE – Nitrofurans derivatives

Nitrofurantoin – J01XE01

It is a synthetic nitrofuran derivative. Patented in 1950.

Systematic revision

- Ben David et al (1995): review of studies available in Medline and from other reliable sources in literature. Of the 22 studies taken in consideration, 4 were cohort studies. 157 exposures altogether were chosen that met the quality criteria established by the authors (Nesbitt and Young 1957, Heinonen et al 1977, Heiley et al 1983, Pellegrini and Koren 1994). Homogenous results were noticed in the 4 studies: cumulative OR for congenital anomalies = 1.3 (CI 95%: 0.3-6.6).

Case-control studies, nonspecific

- Czeizel et al (2001) Hungarian CCSCA: cases: 22,865 newborns with congenital anomalies; controls: (a) 38,151 healthy newborns and (b) 812 infants with Down syndrome. 1,079 exposed cases vs. 774 healthy controls: OR = 2.4 (CI 95%: 2.2-2.6), vs. 23 Down controls: OR = 1.7 (CI 95% 1.1-2.7).

Retrospective cohort studies with internal controls

- Rosa (1993), Michigan MSS: 1,292 first trimester exposures, 52 newborns with major defects, 55 expected: RR = 0.9 (CI 95%: 0.7-1.2).

Nested case-control studies, specific in the prospective cohort of all newborns

- Kallen and Otterblad Olausson (2003): cases: 5,015 newborns with cardiovascular defects, 30 of which exposed to nitrofurantoin in the first trimester; 577,730 controls, 2,060 of which exposed. OR for defects CVS = 1.7 (CI 95%: 1.2-2.4) with 2 cases of coarctation of the aorta vs. 0.4 expected. The author reckoned that such a result is a possible hypothesis to be taken in consideration, since an analogous observation has emerged from a study carried out in Baltimore-Washington, suggesting a remote association with coarctation of the aorta.

Feto-neonatal effects: 1,700 exposures at various stages of pregnancy with no adverse outcomes on the fetus/newborn (Norwich-Eathon 1981).

Conclusions: There are enough studies to prove a lack of evidence for an association between the use of nitrofurantoin in human pregnancy and an

increased reproductive risk. The hypothesis raised by a Swedish study of an association with cardiovascular defects should be reconsidered. The use of this drug in late pregnancy is not recommended, due to the possibility of glucose 6-phosphate-dehydrogenase deficiency causing hemolytic anemia in the newborn (Powel et al 1963, Monkus et al 1969, Gait 1990, Bruel et al 2000).

J01XX – More antibacterial drugs

Phosphomicine – J01XX01

This is a natural antibiotic (*Streptomices fradiae*). Patented in 1968.

Case report

- Forest Laboratories (1997): 2 healthy newborns exposed in the first trimester.

Prospective cohort studies without controls

- Wilton et al (1998): 2 healthy newborns exposed in the first trimester.

Studies on laboratory animals

- Koeda and Moriguchi (1979 a and 1979 b): nonteratogenic in rats and rabbits.

Feto-neonatal effects: This drug has been used after the first trimester in the treatment of bacteriuria during pregnancy. No adverse outcomes have been notice on the newborn (Ruiz Garcia et al 1977, De Cecco and Ragni 1987, Thoumsin et al 1990, Zinner 1990, Reeves 1992, Stein 1998, Kremery et al 2001).

Clofoctolo – J01XX03

This is a synthetic antibacterial drug. Patented in 1968.

We have been unable to locate references on possible human reproductive effects of this agent, or have we found any similar studies on laboratory animals.

Spectinomycin – J01XX04

This is a natural antibiotic (*Streptomyces spectabilis*). Patented in 1965.

Cohort studies without controls

- Cavenee et al (1993) - controlled clinic trial: 20 healthy newborns exposed in the first trimester for maternal gonorrhea.

Feto-neonatal effects: spectinomycin has been used after the first trimester in the treatment of gonorrhea during pregnancy. No adverse outcomes on newborns have been detected (Brocklehurst 2000), or any increase in congenital anomalies, in 49 infants exposed after the first trimester (Cavenee et al 1993).

J01XX class conclusions: We have not been able to find any specific study concerning the use in pregnancy of drugs in this therapeutic group. In case of exposure, the following issues should be considered: absence of reported anomalies over the long period of commercialization, although a limited use in pregnancy is likely, and lack of teratogenic effects in laboratory animals.

J02A – Antimycotics for systemic use

Ketoconazole – J02AB02 – C01CAC08

This is an imidazole derivative. Its structure is related to miconazole and econazole. When administered to men it may decrease plasma levels of testosterone and suprarenal answer to ACTH, inhibiting the synthesis of steroids in gonadal and suprarenal activity (De Felice et al 1981, Pont et al 1984, and Stock 1995). Theoretically this mechanism might change the differentiation of fetal sexual organs (Sonino 1984 and King et al 1998), but the doses of 200 and 400 mg/day have not been associated with failure in the synthesis of steroids (McGregor and Pont 1990). Patented in 1978.

Case report

- Lind (1985): 1 newborn with hydrops fetalis and limbs hypoplasia, exposed from conception to the 7th week of gestation
- Janssen (1988), French Manufacturer: 1 still birth at 38 weeks with absence of upper limbs, facial dysmorphism with retrognathia, clinodactyly of the right foot and small stomach, exposed for maternal psoriasis in the first trimester.
- Amado et al (1990): 1 healthy male infant (with no genital anomalies or symptoms of suprarenal failure) exposed from 1st to 3rd week and from 7th to 37th week for maternal Cushing syndrome.
- Berwaerts et al (1999): 1 male healthy infant (with no genital anomalies or symptoms of suprarenal failure) exposed from 1st to 3rd week and from 7th to 37th week for maternal Cushing syndrome.

Retrospective cohort studies without controls

- Janssen (1989), USA Manufacturer: 40 healthy newborns (2 twins pairs), 2 newborns with congenital anomalies (S.Holt-Oram; acondroplasia) not attributable to a teratogenic effect

Retrospective cohort studies with internal controls

- Rosa (1993), Michigan MSS: 20 first trimester exposures, none of the newborns had major defects.

Prospective cohort studies without controls

- Vial et al (1992), 2 TIS and French Janssen: 53 pregnancies exposed in the first trimester: 22 VIP, 7 miscarriages and 24 healthy newborns one of whom showing palpebral edema and mongolian spot.

Conclusions: There are few available studies and they do not show any association between ketoconazole and reproductive risk increase. In case of exposure such a risk is not likely, due to the lack of reported specific anomalies over the long period of commercialization. Studies on laboratory animals have uncovered teratogenicity of the drug at doses much higher than those used in human therapies. The inhibition of the synthesis in gonadal and suprarenal steroids might change the differentiation of fetal sexual organs and for this reason the drug should be used with caution during pregnancy (McGregor and Pont 1984, Sonino 1987, King et al 1998).

Fluconazole – J02AC01

This is a bis-triazolic derivative of propanol. It is available in Italy since 1989.

Case report

- Lee et al (1992): 1 newborn showed similar defects to those found in Antley-Bixler syndrome (brachycephaly, hypoplasia of nasal bones, craniosynostosis, cleft palate, radio-humeral synostosis, camptomelia and fracture of the femur, and digit anomalies). The syndrome appeared autosomal recessive and the infant had been exposed prior to conception throughout pregnancy to 400 mg/day.
- Pursley et al (1996): 3 newborns (2 brothers) exposed in the first trimester had craniofacial, skeleton and cardiac defects. One of them had already been described (Lee et al 1992). The brother had been exposed to 400 mg/day for 24 weeks; he showed cleft lip, tracheomalacia, facial dysmorphism, clavicle fracture, thin bones, arachnodactyly, defect of the intraventricular septum of heart and pulmonary hypoplasia. The third infant had been exposed to 800 mg/day during the first seven weeks of gestation and from week 9 to birth. He had brachycephaly, trigonocephaly, facial dysmorphism, femoral fracture, thin bones, diffused osteopenia, tetralogy of Fallot, hypoplasia of pulmonary artery, persistent ductus arteriosus and oval foramen of sphenoid bone.
 - Rosa (1996), FDA: 1 newborn with craniofacial and skeletal multiple congenital anomalies exposed in the first trimester to high doses (800 mg/day). 3 newborns with cleft palate, 1 fetus with skeletal defects, 1 newborn with hydrocephaly, 1 with omphalocele and 1 with deafness.
- Aleck and Bartley (1997): 1 newborn with craniofacial and skeletal multiple congenital anomalies exposed in the first trimester to 400 mg/day at 4th and 5th week, then to 800 mg/day until week 9 (case described also by Rosa 1996).
- Sanchez and Moya (1998): 1 newborn exposed at conception to 150 mg had encephalocele and cardiac defects.

Retrospective cohort studies without controls

- Pfizer (1991), manufacturer: 13 exposures: 6 healthy newborns, 1 miscarriage and 6 VIP (one case of anencephaly but 3 former pregnancies of the woman had turned out 1 miscarriage, 1 fetus with anencephaly and 1 healthy infant).

Prospective cohort studies without controls

- Rubin et al (1992): 37 newborns exposed during pregnancy to one single dose of 150mg; 6 newborns exposed at various weeks (some totally inconsistent with a teratogenic effect) had congenital anomalies: bilateral hydronephrosis, light hypospadias, hypospadias with bifid scrotum, digit anomalies, anencephaly and trisomy 18.
- Inman et al (1994): 44 healthy newborns exposed at not specified periods to doses between 50 and 300 mg.
 - Wilton et al (1998): 37 healthy newborns exposed in the first trimester to a single dose of 150 mg
 - Campomori and Bonati (1977), TIS in Italy: 17 healthy newborns exposed to a single mean dose of 291 mg

Retrospective cohort study with internal controls

- Sorensen et al (1999), PEP Database North Jutland: 121 exposures in the first trimester, 13,327 controls. 4 exposed newborns with congenital anomalies vs. 697 among controls. OR = 0.7 (CI 95%: 0.2-1.8).
- Jick (1999), Seattle GHC: 234 exposures in the first trimester to fluconazole, 492 to topic azole, 88 to oral azole, 1,692 not exposed. OR for congenital anomalies in exposures to fluconazole 1.1 (CI 95%: 0.4-3.3), for exposures to oral azole 2.1 (CI 95%: 0.7-6.8), for topic azole 0.6 (CI 95%: 0.2-1.6).

Prospective cohort studies with internal controls

- Mastroiacovo et al (1996), 3 Italian TIS: 226 exposures to fluconazole in the first trimester, mean dose of the single administration 200 mg, 452 controls (newborns exposed to drugs well known to be not associated to a risk increase of congenital anomalies). OR for congenital anomalies = 1.1 (CI 95%: 0.4-2.8), for miscarriage = 1.2 (CI 95%: 0.7-2.2), for still birth = 0.4 (CI 95%: 0.0-3.9), for preterm birth = 1.7 (CI 95%: 0.5-5.0).

Conclusions: Available studies concerning exposure to fluconazole in the first trimester to doses as high as 400 mg/day taken over long periods show an association with a specific malformative pattern similar to the one observed for Antley-Bixler syndrome (cranial stenosis, nasal hypoplasia, cleft lip, bone fusion of limbs, cardiopathy). The risk magnitude of this pattern cannot be assessed. The teratogenic effect is also consistent with the observation that some cases of the syndrome of Antley-Bixler may be attributed to a defect of cholesterol biosynthesis in the lanosterol 14-alpha-demethylase, which is in fact inhibited by fluconazole (Kelley et al 2002). Some cases of the syndrome have uncovered mutations of the POR gene that codifies cytochrome P450 oxidoreductase (Fluck et al 2004).

Itraconazole – J02AC02

This is a triazole-substituted antimycotic. It is available in Italy since 1992.

Case report

- Chotmongkol and Sookprasert (1990): 1 healthy newborn exposed in the first trimester
- Rosa (1996), FDA: 14 reported congenital anomalies, 4 of which relevant to limbs.

Prospective cohort studies without controls

- Wilton et al (1998): 41 exposures to itraconazole in the first trimester: 30 healthy newborns, none of the newborns showed congenital anomalies

Prospective cohort studies with internal controls

- Bar-Oz et al (2000), TIS Motherisk Program: 156 newborns exposed in the first trimester, 187 controls: 5 newborns of the exposed group and 9 among the controls showed congenital anomalies. RR for congenital anomalies = 0.7 (CI 95%: 0.2-2.0).

Conclusions: There is no evidence of association between itraconazole at low doses and risk increase in congenital anomalies. Its analogies with fluconazole – another azolic antimycotic drug (See) – suggest teratogenicity at high doses.

J04 – Antimycobacterial agents

J04A – Drugs for the treatment of tuberculosis

Retrospective cohort studies without controls

- Marcus (1967): of 19 infants born to mothers treated with anti-tubercular drugs, 4 had minor malformations (umbilical hernia and retained testis).
- Bobrowitz (1974): of 42 first trimester exposures to various anti-tubercular agents, 8 newborns had minor defects. Some of the children were followed up for nine years and no adverse effects were detected.
- Steen and Stanton-Ellis (1977): out of 202 pregnancies exposed to anti-tubercular drugs (rifampin, ethambutol and isoniazid), 9 newborns (4.4%) had congenital anomalies (1 anencephaly, 2 hydrocephaly, 4 limb reduction defects, 1 renal malformation and 1 hip dysplasia).

Retrospective cohort studies with internal controls

- Varpela (1964): 123 exposures to anti-tubercular agents (streptomycin, isoniazid and para-aminosalicylic acid combined in different ways), 223 controls. 12 newborns showed congenital anomalies vs. 8 among controls. RR = 2.7 (CI 95%: 1.1-6.5). Results should be interpreted in consideration of the following issues. (a) although the observed malformations were of different kind, they did not show any specific pattern; (b) 6 out of 12 newborns showing congenital anomalies had been exposed after the first trimester; (c) some women had been exposed to different drugs. The author himself is cautious in suggesting a possible association.
- Marynowski and Sianozecka (1972): 1,619 exposed to various anti-tubercular drugs were matched with as many non-exposed infants. RR = 0.9 /CI 95%: 0.6-1.4)

Case-control studies, nonspecific

- Czeizel et al (2001), Hungarian CCSCA: 22,865 newborns with congenital anomalies, 38,151 healthy newborns. 11 cases exposed to anti-tubercular agents vs. 29 healthy controls: OR = 0.6 (CI 95%: 0.3-1.3).

Rifampin – J04AB02

This is a semi-synthetic antibiotic derived from rifamycin B. Patented in 1964.

Literature review

Snider et al (1980): 15 cohort studies were reviewed: 446 exposures, 109 of which in the first trimester of gestation. Miscarriage incidence: 1.7%; congenital defects: 3.4%.

Retrospective cohort studies with internal controls

- Rosa (1993), Michigan MSS: 20 exposed in the first trimester, none of the newborns had major defects.

Feto-neonatal effects: Its intake late in pregnancy may interfere with the synthesis of prothrombin and cause hypothermia and neonatal hemorrhages (Frahm 1976, Eggermont et al 1976). No adverse effect arose in exposed at various stages of pregnancy (Sensi 1971, Jentgens 1975, Bental et al 1995, Hellmeyer et al 2002).

Conclusions: The available studies concerning first-trimester exposure do not reveal an increase in the population background reproductive risk. It should not be used late in pregnancy, due to possible interference with prothrombin synthesis. It is instead recommended in the treatment of tuberculosis during pregnancy (Joint Tuberculosis Committee of British Thoracic Society 1998, Omerod 2001).

Rifabutin – J04AB04

This is a long acting semisynthetic antibiotic, derivative of rifampin B. Patented in 1979

We have been unable to locate references on possible human reproductive effects of this agent, or have we found any similar studies on laboratory animals.

Conclusions: No specific studies have been found in literature relevant to the use of rifabutin in human pregnancy. In case of exposure an increase in the population background reproductive risk is not likely, due to its pharmacological analogy with rifampin, the lack of reported anomalies over the long period of commercialization and the absence of teratogenic effects on laboratory animals (records provided by manufacturers, not available in databases).

Isoniazid – J04AC01

This is a hydrazine of isonicotinic acid. Patented in 1952.

Review of cohort studies without controls

- Briggs et al (2002) reports that the retrospective research of over 4,900 exposed pregnancies has uncovered that the incidence of congenital anomalies in exposed babies is similar to the incidence observed in general among human population (0.7-2.3%).

Case report

- Monnet et al (1967): 5 children were observed, showing severe encephalopathies (4 with mental retardation and convulsions and 1 with spastic hemiplegia). Apparently, the sole possible cause for such anomalies – as suggested by the author – might be hypovitaminosis following exposure to isoniazid at different stages of pregnancy (2 in the first trimester, 3 in the 2nd-3rd trimester).
- Weinstein and Dalton (1968): 4 infants exposed in the first trimester had psychomotor retardation and electroencephalogram alterations.

Retrospective cohort studies with internal controls

- Rosa (1993), Michigan MSS: 11 first trimester exposures, 1 newborn with major defect (polydactyly), 0.5 expected: RR = 2.0 (CI 95% 0.0-11.1).

Prospective cohort studies with internal controls

- Heinonen et al (1977), CPP: 85 exposures in the early 16 weeks, 10 newborns with congenital defects: ARR = 2.6 (CI 95%: 1.5-4.7).

Feto-neonatal effects: 1 case of malignant mesotelioma was observed in a 9-years old child who had been exposed in the 2nd-3rd trimester. Studies on animals have suggested a possible carcinogenic effect (Tuman et al 1980). None of the 660 exposed infants, followed up until 16 years of age, have revealed carcinogenic effects (Hammond et al 1967).

Conclusions: All available studies on exposure to isoniazid in the first trimester, briefly and informally reviewed by Briggs et al (2002), do not suggest an increase

in the population background risk. The study by Heinonen et al (1977) is not sufficient to contradict such a statement, since no similar defects or common pattern have been pointed out among the 10 observed malformations. Besides, the size of the study is compatible with positive results from multiple matching. The reported adverse outcomes in the CNS cannot be disregarded, in consideration of the well-known neuro-toxicity of isoniazid in humans. Nonetheless isoniazid is considered a drug of choice in the treatment of tuberculosis during pregnancy, due to positive evaluation of the risk/benefit ratio, but 50 mg/day of pyridoxine should be administered along with the drug, to prevent possible adverse outcomes in the CNS. (Barclay 1981, American Thoracic Society 1986, Medchill and Gillom 1989, Joint Tuberculosis Committee of British Thoracic Society, 1998, Ormerod 2001, Bothamley 2001).

Pyrazinamide – J04AK01

This agent is structurally similar to nicotinamide. Patented in 1936.

We have been unable to locate references on possible human reproductive effects of this agent, or have we found any similar studies on laboratory animals.

Feto-neonatal effects: no adverse effects on infants exposed after the first trimester Yip et al 1999).

Conclusions: No specific studies have been found in literature concerning the use of this drug in human pregnancy. In case of exposure an increase in the population background reproductive risk is not likely, in consideration of the pharmacological characteristics. Also, the failure to report anomalies over the long period of commercialization and the absence of teratogenic effects in laboratory animals should be considered (records provided by manufacturer, not available in databases).

Ethambutol – J04AK02

Patented in 1960.

Literature review

- Snider et al (1980): 15 cohort studies were reviewed. 630 exposures, 320 of which in the first trimester. The incidence of congenital anomalies was of 2.2%.

Case report

- Perz (1987): 1 newborn exposed in the first trimester with monolateral anophthalmia.
- Roy (1990): 1 newborn exposed in the first trimester with eye defects (microphthalmia and anophthalmia).

Cohort studies without controls

- Potworowska et al (1966): of 23 exposures at various periods of pregnancy, 3 newborns showed not specified congenital anomalies.

Retrospective cohort studies with external controls

- Jentgens (1975): 182 first trimester exposures to rifampin and/or ethambutol. There was no increase in the number of congenital anomalies among newborns.

Conclusions: There are various specific studies in literature concerning the use of ethambutol in human pregnancy. In case of inadvertent exposure an increase in the population background reproductive risk is not likely, due to the lack of

reported anomalies in the long period of commercialization and the absence of teratogenic effects in laboratory animals (records provided by manufacturer, not available in databases). Ethambutol is recommended in the treatment of tuberculosis during pregnancy (Joint Tuberculosis Committee of British Thoracic Society 1998, Ormerod 2001).

J05 – Antiviral agents for systemic use

J05A – Antiviral agents directly acting

J05AB – Nucleosides and nucleotides, inhibitors of reverse transcriptase not included

When these agents are activated by a viral thymidine kinase block the synthesis of viral DNA by means of competitive inhibition of the virus DNA polymerase.

Acyclovir – D06BB03 – J05AB01 – S01AD03

This drug is available in Italy since 1985.

Case report

- Gubbels (1991): diastematomyelia was reported in a fetus exposed over peri-conception to acyclovir, and aborted after prenatal diagnosis.

Prospective cohort studies without controls

- Wilton et al (1998): of 24 exposures in the first trimester of pregnancy, 18 healthy newborns, 1 miscarriage and 5 VIP.
- Stone et al (2004), Acyclovir Registry (1984-1999). The study includes surveys by Andrews et al (1992) and by CDC (1993) Reiff-Eldridge et al (2000). 596 live births were collected according to prospective criteria, exposed to acyclovir by systemic way (out of 756 exposures altogether) during the first trimester of gestation; 19 of them showed various types of congenital anomalies (3.2%, CI 95%: 2.0-5.0). 259 infants were retrospectively collected and 34 of them had various types of congenital anomalies. No evidence of recurrent pattern or of teratogenic effect was detected in the analysis carried out as per single month of exposure.

Retrospective cohort studies with external controls

- Ratanajamit et al (2003), PEP Database North Jutland: 90 exposures by systemic way at various stages of pregnancy and 995 topic exposures, and as many controls. OR for congenital anomalies systemically exposed = 0.7 (CI 95%: 0.2-2.8), topically = 0.8 (0.5-1.4); OR for low weight in systemic exposures = 2.0 (0.5-4.8); OR for miscarriage in systemic exposure = 2.2 (0.6-7.8).

Retrospective cohort studies with internal controls

- Rosa (1993), Michigan MSS: 478 first trimester exposures, 18 newborns with major defects, 20 expected: RR = 0.9 (CI 95%: 0.5-1.4).

Feto-neonatal effects: no adverse outcomes in exposures after the first trimester (Lagrew et al 1984, Grover et al 1985, Chazotte et al 1987, Cox et al 1987, Hankey et al 1987, Frieden et al 1990, Stray-Pedersen 1990, Smego et al 1991, Glorioso et al 1996, Scott et al 1996, Brocklehurst et al 1998, Glaxo 1999).

Ganciclovir – J05AB06

It is available in Italy since 1997.

We have been unable to locate references on possible human reproductive effects of this agent.

Studies on laboratory animals

- Hartmann et al (1991): teratogenic in rats (testicular hypoplasia, hydrocephaly, renal agenesis, and hepatic and skeletal malformations).

Case report

- Miller et al (1995), Pescovitz (1999): 2 healthy newborns exposed throughout pregnancy.

Feto-neonatal effects: no adverse effects on 3 infants exposed after the first trimester (Pescovitz 1999).

Famciclovir – J05AB09

It is available in Italy since 2002.

Prospective cohort studies without controls

- Wilton et al (1998): 7 exposures in the first trimester of pregnancy: 4 healthy newborns, 3 miscarriages.

Valacyclovir – J05AB11

It is converted into acyclovir, and it is its precursor. It is available in Italy since 1998.

Cohort studies without controls

- Glaxo (1999), Valacyclovir Registry (1995-1999): 191 first trimester systemic exposures: 29 cases prospectively collected (21 healthy newborns, 1 clubfoot, 2 miscarriages and 2 VIP) and 14 cases retrospectively collected (3 healthy newborns, 3 miscarriages and 8 VIP).

Feto-neonatal effects: no adverse effects on infants exposed after the first trimester (Glaxo 1999).

J05AB class conclusions: None of the available studies on acyclovir and valacyclovir (its precursor) suggest an increase in the reproductive risk. As far as ganciclovir and famciclovir are concerned, there are limited studies and the sole information we can deduce is that there is no increase in reproductive risk.

J05AD – Phosphonic acid derivatives

They interfere with the activity of viral DNA polymerase acting as competitive inhibitors of natural or alternative substrates causing the blockage of the viral chain lengthening.

Foscarnet – J05AD01

It is nephrotoxic in adults. It is available in Italy since 1993.

We have been unable to locate references on possible human reproductive effects of this agent, or have we found any similar studies on laboratory animals.

Feto-neonatal effects: no adverse effects were detected in a newborn exposed after the first trimester (Alvarez-McLeod et al 1999).

Conclusions: The lack of studies on first-trimester human exposures does not draw to any conclusion. Skeletal defects observed in studies on laboratory animals (rats and rabbits) concerning teratogenicity do not enable us to point out specific results.

J05AF – Nucleosides inhibiting reverse transcriptase

These agents inhibit DNA polymerase RNA-dependent (reverse transcriptase of HIV) blocking acute cell infection but they have little influence on chronically infected cells. They are normally used in combination between themselves and/or with others antiretroviral medications in the treatment of the related HIV pathology and to prevent maternal-fetal transmission of HIV virus.

Case report

- Blanche et al (1992): 2 newborns exposed to didanosine, lamivudine and zidovudine throughout pregnancy. One had chronic lactic acidosis and mitochondrial disorder causing convulsions, tetraparesis and cognitive dysfunction, and, eventually, death at eleven months. The other had biochemical changes suggesting mitochondrial disorder on retina and CNS, without symptoms.

Retrospective cohort studies with internal controls

- De Santis et al (2003), TIS Telefono Rosso: 3 hemangiomas and one spina bifida out of 71 newborns exposed to antiretroviral therapy for maternal HIV, observed from 1997 to 2002. The three hemangiomas had been exposed to zidovudine, lamivudine and nelfinavir. 5 congenital anomalies were detected in the control cohort (284 newborns), one of them being a hemangioma.

Zidovudine (AZT) – J05AF01

It is available in Italy since 1995.

Cohort studies without controls

- Sperling et al (1992): 12 newborns exposed in the first trimester, 1 of whom showing high levels of 17a-OH progesterone (normalized at 4 months) and clitoral hypertrophy.
- Kumar et al (1994): 104 exposed newborns, 49 of whom in the first trimester and 4 out of the latter had unlike congenital anomalies (2 newborns showed minor multiple defects; polydactyly + cleft palate and harelip; feto-alcoholic syndrome).
- Richardson et al (2000): 2 HIV-positive pregnancies, 1 newborn with lumbar hemivertebra exposed in the first trimester to co-trimoxazole, zidovudine and zalcitabine, 1 newborn with spina bifida exposed in the first trimester to co-trimoxazole, didanosine, stavudine and nevirapine.
- Antiretroviral Pregnancy Registry (2003): 1989-2003: prospective cohort of 1,003 live births exposed in the first trimester to zidovudine alone or along with other antiretroviral agents. 27 out of the total (2.7%, CI 95%: 1.8-3.9) had congenital defects without a specific pattern. Of 730 exposed in the 2nd and 3rd trimester, 16 (2.2%) had congenital anomalies. The registry data suggest that RR be lower than 1.5 for congenital anomalies in general, for cardiopathies and defects of the genital-urinary system.

Retrospective cohort studies with internal controls

- Rosa (1993), Michigan MSS: 2 healthy newborns exposed in the first trimester.
- Newschaffer et al (2000), New York Medicaid: 1,932 live births to HIV-positive mothers: AOR for any type of congenital anomalies and at each stage of pregnancy = 1.5 (CI 95%: 1.0-2.3). Each trimester of exposure was analyzed: in the 1st trimester AOR = 1.2 (CI 95%: 1.0-2.3), 2nd trimester = 1.5 (CI 95%: 0.9-2.6), 3rd trimester = 1.8 (CI 95%: 1.0-3.3) and no teratogenic effect was detected. In the analysis carried out as per subgroups,

OR for central nervous system defects in infants exposed during the 1st trimester of pregnancy vs. non-exposed = 8.0 (CI 95%: 1.6-37.5).

Feto-neonatal effects: neonatal anemia (Watson et al 1988, Sperling et al 1992, Connor et al 1994, Lorenzi et al 1998 and Mandelbrot et al 2001); neutropenia (Mandelbrot et al 2001); mitochondrial toxicity (Blanche et al 1999, Stojanov et al 2000, Barrett et al 2003). Pathological effects on the central nervous system and myocardium were detected in less than 1% of the cases. Transitory intestinal sub-obstruction was also found (Neuman et al 1998) and acute lymphoblastic leukemia, which arose at 6 months of age (Moschovi et al 2000). No cardiac toxicity (Lipshultz et al 2000), no tumor pathology in follow-up until 14-38 months of age (Hanson et al 1999). No impairments in psychophysical growth was noticed, no tumor pathology, no ophthalmic anomalies in follow-up until 4 years of age (Culnane et al 1999). Oral pre-birth treatment and intra-partum treatment via *ev* has been carried out in HIV-positive women at 14th-34th week of gestation as a clinic trial, has successfully put down the risk of vertical transmission of the virus to 67.5% (CI 95%: 40.7%-82.1%).

Zalcitabine – J05AF03

It is available in Italy since 1995.

Cohort studies without controls

- Antiretroviral Pregnancy Registry (2000), 1989-2000: prospective cohort of 38 live births exposed to zalcitabine (7 of them took it alone) alone or along with other antiretroviral agents in the first trimester. One of them had a not specified congenital anomaly.

Feto-neonatal effects: neonatal anemia (Watson et al 1988). See also zidovudine.

Lamivudine – J05AF05

It is available in Italy since 1996.

Cohort studies without controls

- McGowan et al (1999): of 29 exposures throughout all pregnancy, 23 healthy newborns, 1 stillbirth, 4 underweight infants and 1 microcephaly.
- Antiretroviral Pregnancy Registry (2000) 1989-2000: prospective cohort of 367 newborns exposed to lamivudine (6 of them took it alone) alone or along with other antiretroviral agents in the first trimester. Only seven of them had congenital anomalies.

Feto-neonatal effects: prematurity, anemia, transitory hepatitis, cerebral hemorrhage (Lorenzi et al 1998); transitory anemia (Watson et al 1988). No adverse outcome was detected in newborns exposed late in pregnancy (Moodley et al 1998). See also zidovudine.

J05AF class conclusions: The available studies in literature concerning the use of nucleosides inhibitors of reverse transcriptase do not show an increase in congenital anomalies, or any specific malformation pattern. The benefit obtained in decreasing the vertical transmission of HIV virus is higher than the possible risk of mitochondrial toxicity (the sole adverse documented effect). It is worth of notice the hypothesis arisen by Newschaffer et al (2000) relevant to a possible association with CNS defects.

J05AH – Inhibitors of neuramidase

They inhibit superficial viral neuramidase, essential to make infected cell releasing the newly formed viral particles.

Zanamivir – J05AH01

It is available in Italy since 1999.

We have been unable to locate references on possible human reproductive effects of this agent, or have we found any similar studies on laboratory animals.

Conclusions: No specific studies are available in literature concerning the use of zanamivir in human pregnancy and we have no evidence of possible adverse outcomes on fetal growth when exposed to neuramidase inhibitors in the first trimester only. The limited clinical testing recommends its use in pregnancy only for selected cases.

J05AX – More antiviral agents

Lysozyme – J05AX02

This is a polypeptide enzyme naturally existing in human body and it is one of the factors of nonspecific cellular and humoral immunity. It strengthens “in vitro” antibacterial activity of several antibiotics. It is available in Italy since 1951.

We have been unable to locate references on possible human reproductive effects of this agent, or have we found any similar studies on laboratory animals.

Inosine pranobex (methisoprinol) – J05AX05

This agent has direct antiviral activity: it prevents viral replication and it has an immuno-modulating activity, thus increasing the formation and the efficiency of lymphocytes-B and –T. It is available in Italy since 1979.

We have been unable to locate references on possible human reproductive effects of this agent, or have we found any similar studies on laboratory animals.

Neuramide – J05AX49

It inhibits viral replication. It is available in Italy since 1951.

We have been unable to locate references on possible human reproductive effects of this agent, or have we found any similar studies on laboratory animals.

J05AX class conclusions: There is no written evidence of specific studies concerning the use of drugs belonging to this therapeutic group in human pregnancy. In case of exposure an increase in the population-based reproductive risk is not likely, in consideration of pharmacological characteristics. The failure to report anomalies over the long period of commercialization and the absence of teratogenic activity on laboratory animals should also be considered (records provided by manufacturer for registration, not available in databases).

J06 – Immune serums and Immunoglobulins

Human normal immunoglobulins – J06BA01

They derive from human normal plasma, from a pool of a minimum of 1,000 donors, and it contains all immunoglobulin subclasses. They are available in Italy since 1972.

We have been unable to locate references on possible human reproductive effects of this agent, or have we found any similar studies on laboratory animals.

Case report

- Ross (1995): 1 newborn with duodenal stenosis and 1 newborn with hiatal paraesophageal hernia both exposed in the first trimester.

Conclusions: Its use is recommended in case of inadvertent exposure in pregnancy to hepatitis A and rubella (American College Obstetricians Gynecologists 1991).

J06BB Specific Immunoglobulins

Anti tetanus immunoglobulin – J06BB02

It is available in Italy since 1972.

We have been unable to locate references on possible human reproductive effects of this agent, or have we found any similar studies on laboratory animals.

Conclusions: Its use is recommended in pregnancy only in case of suspected infection (American College Obstetricians Gynecologists 1991).

Anti varicella-zoster immunoglobulin – J06BB03

It is available in Italy since 1998.

We have been unable to locate references on possible human reproductive effects of this agent, or have we found any similar studies on laboratory animals.

Conclusions: Its use is recommended within 96 hours from suspected exposure in pregnancy to prevent maternal infection, but not against fetal infection (American College Obstetricians Gynecologists 1991).

Hepatitis B immunoglobulin – J06BB04

It is available in Italy since 1979.

We have been unable to locate references on possible human reproductive effects of this agent, or have we found any similar studies on laboratory animals.

Conclusions: Its use is recommended in case of suspected exposure during pregnancy (American College Obstetricians Gynecologists 1991).

J07 – Vaccines

J07A – Bacterial vaccines

They are vaccines obtained from attenuated microbes, microbe fractions and bacterial toxins. Microbes employed in vaccines are attenuated so as not to provoke the illness. There is a risk in pregnancy that microorganisms contained in the vaccine might not only proliferate in maternal body but also cross the placenta and reach the fetus.

Meningococcus polysaccharide vaccine – J07AH04

This is obtained from the cell wall of killed bacteria. It is available in Italy since 1991.

Cohort studies without controls

- Letson et al (1998): 34 exposures: 4 in the first trimester, 17 in the 2nd and 13 in the 3rd trimester. One single newborn with congenital anomaly (Charlie M syndrome) exposed at 33 weeks.

Feto-neonatal effects: No adverse outcome on newborns exposed in the first trimester (Shahid et al 1995, O'Dempsey et al 1996).

Conclusions: There are very limited studies concerning the use of polysaccharide meningococcus in pregnancy. In case of exposure an increase in the population-based reproductive risk is not likely. The American College of Obstetricians and Gynecologists (1991), WHO (2002) and the Royal College of Obstetricians and Gynecologists (2003) recommend its use in pregnant women only in the case of high risk.

Adsorbed tetanus vaccine – J07AM01

This is a tetanus anatoxin, specific toxoid of Clostridium tetanus. It is available in Italy since 1961. (From REPROTOX: Tetanus toxoid is derived from the inactivated toxin of Clostridium tetanus.)

Case-control studies, nonspecific

- Silveira et al (1995), ECLAMC: 34,293 cases showing congenital anomalies and 34,477 healthy controls were matched as per sex, hospital and date of birth. Post-axial polydactyly revealed OR of 1.8 (CI 99%: 1.3-33) out of 10 different types of defects detected in a survey of 1,000 cases.
- Czeizel and Rockenbauer (1999), Hungarian CCSCA: 21,563 cases of newborns with congenital anomalies, 25 of which exposed, and 35,727 healthy newborns, 33 of which exposed. OR = 1.3 (CI 95%: 0.7-2.2).

Prospective cohort studies with internal controls

- Heinonen et al (1977, CPP: 337 exposures in the early 16 weeks, 17 newborns with congenital anomalies: ARR = 1.1 (CI 95%: 0.7-1.8).

Feto-neonatal effects: One single case-control study out of 100 women who had had a miscarriage and had been exposed to tetanus vaccine within the early 19 weeks of pregnancy turned out negative (Cating et al 1996). There is an increased frequency of infants bearing jaundice from ABO incompatibility, born to O blood group women. This is probably due to an increase in the titer of anti-A and anti-B normally occurring after vaccination (Gupte and Bathia 1980).

Conclusions: We have as many good quality studies on this drug as to confirm that there is no evidence of association between tetanus anatoxin and population-based risk increase. The American College of Obstetricians and Gynecologists (2003) recommend its use during pregnancy, if necessary.

Adsorbed diphtheria vaccine – J07AM51

This is a specific toxoid of *Corynebacterium diphtheriae*. It is available in Italy since 1985.

Prospective cohort studies with internal controls

- Heinonen et al (1977, CPP: of 75 exposures in the early 16 weeks, 1 newborn with congenital anomalies. ARR = 0.3 (CI 95%: 0.0-2.0).

Conclusions: Very limited specific studies have been located in literature on the use of diphtheria vaccine in pregnancy. Nonetheless, an increase in population-based reproductive risk is not likely, in consideration of its biological characteristics and the failure to report anomalies over the long period of commercialization. The American College of Obstetricians and Gynecologists (1991) and the Royal College of Obstetricians and Gynecologists (2003) recommend its use during pregnancy, when needed.

Tuberculosis vaccine – J07AN01 – L03AX03

This attenuated live vaccine is available in Italy since 1994.

We have been unable to locate references on possible human reproductive effects of this agent, or have we found any similar studies on laboratory animals.

Conclusions: There is no written evidence of specific studies concerning the use of this agent in human pregnancy. An increase in the population-based reproductive risk is not likely, due to a lack of reported anomalies over the long period of commercialization.

Typhoid vaccine – J07AP01

There are two types of immunizing preparations: the first is prepared with live attenuated bacteria and orally administered, the latter is a typhoid-paratyphoid preparation made of lysate bacterial antigens adsorbed to aluminum hydroxide. They are available in Italy since 1984.

Prospective cohort studies with internal controls

- Heinonen et al (1977), CPP: of 44 exposures in the early 16 weeks to typhoid vaccine prepared with killed bacteria, 1 newborn had congenital anomalies. ARR = 0.5 (CI 95%: 0.0-3.5).
- Mazzone et al (1994), Italian TYS: 21 newborns exposed to orally administered typhoid vaccine (attenuated live bacteria) in the first trimester and 183 controls. 14 healthy newborns; 1 newborn exposed also to tetanus toxoid and chloroquine, with vesicle-urethral reflux of III type (!??). RR = 2.0 (CI 95%: 0.3-15.8).

Conclusions: The available studies are too limited to suggest an association with typhoid live or oral attenuated vaccine. In case of exposure an increase in the population-based reproductive risk is not likely, due to a lack of reported anomalies over the long period of commercialization and considering its biological characteristics. Its use is recommended in pregnancy in case of exposure or travelling to endemic areas (American College Obstetricians Gynecologists 1991).

Polysaccharide typhoid vaccine – J07AP03

This is an antigen. It is available in Italy since 1996.

We have been unable to locate references on possible human reproductive effects of this agent, or have we found any similar studies on laboratory animals.

Conclusions: There are not specific studies in literature concerning the use of this vaccine in human pregnancy. In case of exposure an increase in the population-based reproductive risk is not likely, due to the lack of reported anomalies over the long period of commercialization and considering its biological characteristics.

J07AX – More bacterial vaccines

Bactolysate – J07AX

This is a bacterial lyophilized lysate. It is available in Italy since 1993.

We have been unable to locate references on possible human reproductive effects of this agent, or have we found any similar studies on laboratory animals.

Escherichia coli lysate – C05AX49 – J07AX

It is a bacterial lysate.

We have been unable to locate references on possible human reproductive effects of this agent, or have we found any similar studies on laboratory animals.

Klebsprotina – J07AX

This is a protein obtained from Klebsiella pneumoniae. It is available in Italy since 1988.

We have been unable to locate references on possible human reproductive effects of this agent, or have we found any similar studies on laboratory animals.

Ribosomal – J07AX

Bacterial ribosomal fractions. It is available in Italy since 1995.

We have been unable to locate references on possible human reproductive effects of this agent, or have we found any similar studies on laboratory animals.

Pneumo-catarrhal oral vaccine – J07AX

It is available in Italy since 1974

We have been unable to locate references on possible human reproductive effects of this agent, or have we found any similar studies on laboratory animals.

Staphylococcus vaccine – J07AX

This is a bacterial lysate. It is available in Italy since 1965.

We have been unable to locate references on possible human reproductive effects of this agent.

Studies on laboratory animals

- Hyrayama et al (1980) reports that the drug is not teratogenic in rats or rabbits at doses of 2 ml/kg/day and 0.5 ml/kg/day respectively, administered subcutis

J07AX class conclusions: There is no written evidence relevant to the use of drugs in this therapeutic class. In case of exposure an increase in the population-

based reproductive risk is not likely, in consideration of their pharmacological characteristics. The lack of reported anomalies over the long period of commercialization, biological characteristics and the absence of teratogenic activity on laboratory animals should also be considered (records provided by manufacturer for registration, not available in databases).

J07B – Viral vaccines

Inactivated influenza vaccine – J07BB02

This is a surface – with fragmented virus – inactivated antigen (surface adjuvant vaccine). It is available in Italy since 1995.

Case report

- Samat et al (1979): female infant with complex cerebral impairments compatible with the failure of cerebral development during the first trimester of gestation and exposed at week 6 to influenza vaccine. The mother had clear influenza symptoms for two weeks.

Prospective cohort studies with internal controls

- Heinonen et al (1973 and 1977), CPP: of 650 newborns exposed during the early 16 weeks, 27 had congenital anomalies. ARR = 0.9 (CI 95%: 0.6-1.3). Tumor pathologies did not increase during the first 7 years of age.
- Deinard and Ogburn (1981): 189 exposure prior to or during pregnancy, 517 non-exposed controls. No increase in congenital anomalies.

Feto-neonatal effects: there were no adverse outcomes in 2nd and 3rd trimester exposures (Sumaya and Gibbs 1979).

Conclusions: Available studies are not sufficient to deny an increase in the population-based reproductive risk relevant to inactivated influenza vaccine. Centers for Disease Control consider influenza vaccine not causative of risks at no stage of pregnancy (ACIP 2003,2004).

Hepatitis B vaccine – J07BC01

This B purified hepatic antigen (HbsAg) is obtained by means of genetic engineering. It does not contain virus. It is made of an amino-acid sequence able to call for an immune-system response against hepatitis B virus. It is available in Italy since 1987.

Cohort studies without controls

- Levy and Koren (1991): 10 healthy newborns exposed in the first trimester checked (with a follow-up) at 2-12 months.
- Grosheide et al (1933): 6 newborns exposed in the first trimester, 13 exposed later: no congenital anomalies also in the follow-up until 22 months of age.

Conclusions: We have limited studies in literature concerning the use of hepatitis B vaccine in human pregnancy. A population-based reproductive risk increase is not likely, also in consideration of the biologic features of this drug and the lack of reported anomalies over the long period of commercialization. Its use is recommended in pregnancy in case of exposure or when travelling in endemic regions (American College of Obstetricians and Gynecologists 1991). Centers for Disease Control (1991) state that there is no risk of adverse outcomes on the fetus in case of vaccination during pregnancy and that there are no contraindications.

Measles vaccine – J07BD01

This is a live attenuated vaccine. It is available in Italy since 1977.

Prospective cohort studies with internal controls

- Heinonen et al (1977), CPP: none of the 37 newborns exposed in the early 16 weeks of gestation showed congenital anomalies.

Conclusions: Live virus vaccines are not recommended during pregnancy since they might cause fetal infection. Although they do not appear to increase the risk of congenital anomalies, Centers for Disease Control (1998) consider that vaccination is contraindicated during pregnancy. The American College of Obstetricians and Gynecologists (1991), WHO (2002) and the Royal College of Obstetricians and Gynecologists (2003) suggest to delay pregnancy for three months following vaccination.

Measles–mumps–rubella virus vaccines – J07BD52

This is a live attenuated vaccine. It is available in Italy since 1977.

Conclusions: Please refer to single vaccines. WHO (2002) and the Royal College of Obstetricians and Gynecologists (2003) consider pregnancy a contraindication for vaccination. All recent recommendations of CDC reckon that 28 days delay is sufficient for a pregnancy after vaccination against Measles, Mumps and Rubella (CDC 2001).

Mumps vaccine – J07BE01

This is a live attenuated vaccine. It is available in Italy since 1991.

We have been unable to locate references on possible human reproductive effects of this agent, or have we found any similar studies on laboratory animals.

Conclusions: Live virus vaccines are not recommended during pregnancy since they might cause fetal infection. Although they do not appear to increase the risk of congenital anomalies, Centers for Disease Control (1998) consider that vaccination is contraindicated during pregnancy. The American College of Obstetricians and Gynecologists (1991), WHO (2002) and the Royal College of Obstetricians and Gynecologists (2003) suggest to delay pregnancy for three months following vaccination.

Poliomyelitis attenuated oral vaccine – J07BF02

This is a live attenuated trivalent vaccine. It is available in Italy since 1964.

Case Report

- Castleman and McNeely (1964): 1 newborn with bilateral renal dysplasia exposed in the 1st and 2nd trimester
- Burton et al (1984): 1 fetus of 21 weeks showing spinal impairments similar to those provoked by poliovirus (cell lesions of cornu anterius).

Cohort studies with external controls

- Harjulehto et al (1989,1993,1994): Finland 1985, mass vaccination (94% of the population). Cases were all born in 1986, controls in 1984 and 1985. RR for congenital anomalies in 1st trimester exposures = 0.7 (CI 95%: 0.5-1.0).
- Ornoy and Ben Ishai (1993): Israel 1988 mass vaccination (90% of the population). Of 15,696 cases (born in 1989), 243 had congenital anomalies. Of 15,021 controls (born in 1988), 204 had congenital anomalies. RR: 1.1 (CI 95%: 0.9-1.4).

Prospective cohort studies with internal controls

- Heinonen et al (1977), CPP: of 1,628 exposed in the early 16 weeks, 77 newborns showed congenital anomalies. ARR = 1.0 (CI 95%: 0.8-1.3). An

increase in still births and incidence of neural tumors were noticed, among the exposed infants (7.6/10,000) compared to non-exposed (3.1/10,000) (Heinonen et al 1973). Also reported in a study by Farwell et al 1980. Simian virus 40, an oncogenic virus (Marindale 1989), contaminated poliomyelitis vaccine available in the '50s. This virus or other factors might therefore explain the association observed (Rosa et al 1998, Melnick and Butel 1988).

Conclusions: We have enough studies suggesting that there is no evidence of association between inactivated intramuscular poliomyelitis vaccine and population-based reproductive risk increase.

Rabies vaccine – J07BG01

This is an inactivated vaccine, full virus. It is available in Italy since 1980.

Cohort studies without control

- Chutivongse and Wilde (1989): 21 exposures at various stages of pregnancy to passive immunization with equine immunoglobulin and rabies vaccine. 20 newborns without congenital anomalies.
- Chalaba et al (1991): 24 exposures at various stages of pregnancy to passive immunization with equine immunoglobulin and/or rabies vaccine and 1 exposure to specific human immunoglobulins and vaccine from human diploid cells, with no adverse outcomes on fetus/newborn.
- Fescharek et al (1990): 16 exposures during pregnancy to passive immunization with equine immunoglobulin and rabies vaccine. No increase of congenital anomalies in the newborns.
- Chutivongse et al (1995): 202 exposures to passive immunization with equine immunoglobulin and/or rabies vaccine at various stages of pregnancy. No adverse outcomes were noticed on newborns.
- Sudarshan et al (1999): 29 exposures at various stages of pregnancy. No newborns with congenital anomalies.

Feto-neonatal effects: no adverse effects on newborns exposed after the first trimester (Varner et al 1982, Figueroa et al 1994).

Conclusions: We have enough studies suggesting that there is no evidence of association between rabies vaccine and population-based reproductive risk increase.

Rubella virus vaccine – J07BJ01

Wistar RA 27/3 live attenuated vaccine is available in Italy since 1975.

(From REPROTOX: Rubella vaccine contains live, attenuated rubella (German measles) virus from the RA 27/3 strain of this virus.)

Retrospective cohort studies without controls

- Ajjan and Triau (1973): this French study reports 103 newborns to women immune or susceptible to rubella virus, exposed just prior to or soon after conception. None of them suffered from congenital rubella syndrome.
- Anonymous CDC (2001): all cohort studies recently carried out in the USA, Great Britain, Sweden and Germany were considered as a whole. 680 live births to women "susceptible to rubella" inadvertently vaccinated 3 months prior to or early in pregnancy with one of the three rubella virus vaccines (RA27/3, HPV-77 or Cendehill) were surveyed. 293 women exposed between 1-2 weeks prior to and 4-6 weeks after conception were included in the study. None of the newborns showed congenital rubella syndrome or any possibly related defects.
- Hofmann et al (2000): 6 newborns exposed just prior to or soon after conception. None of the newborns had congenital anomalies. Nonetheless one

of them had persistent rubella fetal infection until the end of pregnancy, thus revealing the possibility of vertical infection, even though there were no adverse outcomes

Conclusions: Evidence produced so far by CDC (2001) is good enough and we can state the followings:

- 1.No newborns have been described showing congenital anomalies attributable to rubella virus vaccine.
- 2.The upper limit of IC at 95% has not been observed in any of the 680-exposed cases. On this ground and on the basis of the above mentioned review CDC reckon that the risk for congenital rubella is not lower than 0.5% in case of vaccination with any type of rubella vaccine (RA27/3, HPV-77 or Cendehill) 3 months prior to or during pregnancy. Such a risk rises to 1.3% when the survey is limited to newborns exposed 1-2 weeks prior to and 4-6 weeks following conception. These are the highest figures that can be assumed also considering other published and non-published information.
- 3.It is nevertheless prudent to consider vaccination during pregnancy a contraindication.
- 4.Inadvertent vaccination 3 months prior to conception or during pregnancy should not be causative of any risk and miscarriage is not recommendatory.
- 5.Pregnancy may well be started 28 days after rubella vaccination.

Varicella vaccine – J07BK01

It is an attenuated live vaccine. It is available in Italy since 2000.

Case report

- Salzmar et al (1997): 1 case of varicella transmitted from vaccinated fetus to immune mother. The varicella-zoster virus has not been isolated from the tissues of the fetus aborted by the woman at 7th week of pregnancy.

Cohort studies without controls

- Merck Pregnancy Registry Program (2000), Shields et al (2001) 1995-2000: 509 women vaccinated 3 months prior to pregnancy or during pregnancy. 486 prospective exposures, 23 retrospective exposures. See details in the following Table. Total incidence of defects in newborns 1.8% (7/397). None of the outcomes showed congenital anomalies possibly related to congenital varicella syndrome.

Outcome	Prospective exposures	Retrospective exposures
Lost at follow-up	89	0
Pregnancy termination	25	0
Pregnancy termination With congenital anomalies	2 (trisomy 21; trisomy 18) exposed after last menstruation	2 (holoprosencephaly+LPS ; trisomy 21) exposed before last menstruation
Miscarriages	42	5
Miscarriages with congenital defects	0	1 (cystic hygroma+anasarca +brachydactyly) exposed before last menstruation
Still births	1	0
Healthy newborns	322	13
Newborns with congenital anomalies	5 (hypospadias) exposed before last menstruation (polydactyly; tetralogy of Fallot; hypospadias; preauricular sinus) exposed after last menstruation	2 (encephalocele+CNS defects+ocular defects) exposed after last menstruation; (renal dysplasia) exposed at 28 weeks.

Overall exposures	486	23
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Conclusions: There is no evidence of an association between varicella vaccine and population-based risk increase. For prudential reasons we pregnancy should be postponed to one month after varicella vaccine.