CQ415-3: What should one do after assessing the cardiotocogram results while using uterotonics?

Answer

1 The i.v. dosage can be increased after all of the following conditions are present: (B)
   (i) Insufficient uterine contraction.
   (ii) Level 1 or 2 fetal heart rate pattern (see CQ411).
   (iii) Current dosage has lasted for 30 min or more.
   (iv) Current dose is below 'the maximal dose' (see CQ415-1).
2 Consider the following measures when 'tachysystole' (uterine contractions >5/10 min) occurs: (B)
   (i) Withhold the next oral PGE2 dose.
   (ii) Decrease the infusion rate to half of the current i.v. rate.
3 Do the following in the event of the appearance of an abnormal fetal heart rate pattern (Level 3 or more): (B)
   (i) Withhold the next oral PGE2 dose.
   (ii) Consider withholding the drug or decreasing the infusion rate to half of the current i.v. rate.
4 Promptly record the result of the 'consideration' on the patient's medical chart in cases with Answer 2 or Answer 3-2. (B)
5 Consider withholding the drug or decreasing the dosage when a woman complains of extraordinarily strong pains. (C)

Chapter F. Incidental Complications

CQ501: How should one respond when asked about the outcome of pregnancy complicated by uterine myoma?

Answer

1 Answer as follows:
   (i) The pregnancy outcome is fairly good. (B)
   (ii) There may be increased risks of complications, such as premature labor, an abnormal position of the fetus, placenta previa, placental abruption, poly- or oligohydramnios, pregnancy-induced hypertension, or premature membrane rupture. (B)
   (iii) Some women may experience transient pain (for 1–2 weeks) originating from the myoma. (B)
   (iv) There may be increased risks of dystocia, increased bleeding, labor arrest, and the need for a cesarean delivery. (B)
   (v) The risks and benefits of a myomectomy during pregnancy and a cesarean section are uncertain at present. (C)
   (vi) There may be an increased risk of the need for a hysterectomy post-partum because of the degeneration/infection of the myoma/uterus. (C)

CQ502: How should women with an abnormal uterine cervical cytology result during early pregnancy be treated?

Answer

1 Perform a colposcopy, in principle, and biopsy if necessary for patients with an abnormal cytology (other than NILM in the Bethesda system). (B)
2 Treat women with histologically confirmed cervical intraepithelial neoplasia in the absence of a cell cytology suggestive of invasive cancer conservatively without conization. (B)
3 Perform conization in cases with any of the following characteristics: (A)
   (i) Histologically confirmed microinvasive cancer.
   (ii) Histologically confirmed intraepithelial neoplasia but a cell cytology indicative of invasive cancer.
   (iii) Histologically confirmed adenocarcinoma *in situ*.
4 Conservative treatment without termination of the pregnancy is feasible in cases with both stage Ia1 disease/adenocarcinoma *in situ* and no lymph node or vascular space invasion in the conization specimen. (B)
5 Repeat the cytology examination during pregnancy in women with conservative treatment. (A)
6 Vaginal delivery is feasible in women with conservative treatment. (A)
7 Reevaluate the disease status using cytology, a colposcopy, and a biopsy 4–8 weeks post-partum. (B)

CQ503: How should pregnant women with a postconization uterus be treated?

Answer

1 When asked, tell the client, 'Women are at an increased risk of preterm labor after undergoing cervical conization.' (A)
2 Be cautious of signs of preterm labor, such as the shortening of the uterine cervix and increased uterine activity. (B)
3 Consider therapeutic cervical cerclage in women with a shortened uterine cervix. (C)

CQ504: How should women with an ovarian mass detected during early pregnancy be treated?

Answer

1 Use ultrasonography to visualize the ovarian cyst and assess the possibility of malignancy. (A)
2 Monitor the size of the ovarian cyst to rule out the possibility of a common 'corpus luteum cyst', which may resolve spontaneously. (A)
3 Treat women with ultrasonography findings suggestive of an ovarian cyst appearing as a tumor-like lesion, such as a corpus luteum cyst or an endometriotic cyst, conservatively. (B)
4 Treat women with an ovarian cyst with the characteristic ultrasonographic features of a benign lesion as follows: (C)
   (i) An ovarian cyst with a largest diameter <6 cm or a unilocular ovarian cyst with a largest diameter of <10 cm: conservative treatment without surgical intervention.
   (ii) An ovarian cyst with a largest diameter ≥10 cm or an ovarian cyst except for a unilocular cyst with a largest diameter ≥6 cm: surgical removal of the cyst, preferably after 12 weeks of gestation.
5 Remove the tumor surgically irrespective of the size and gestational age in principal if a borderline or malignant tumor is suspected. (B)
6 Remove the cyst surgically irrespective of the nature of the cyst and the gestational age in cases with severe abdominal pain as a result of ovarian torsion, rupture, or bleeding. (A)

CQ505: How should women with decayed teeth and/or periodontal diseases be treated?
Answers

1 Recommend a visit to a dentist when asked about decayed teeth and/or periodontal diseases, as pregnancy may have an unfavorable effect on the progression of these diseases. (B)

CQ506: Which diseases are rare but potentially fatal during pregnancy?
Answer

1 Note that diseases including fulminant-type infection with group A streptococcus (GAS), fulminant type I diabetes mellitus, aorta dissection, long QT syndrome, pulmonary thromboembolism, amniotic fluid embolism, and peripartum cardiomyopathy are rare but potentially fatal during pregnancy. (C)
2 Note that the following symptoms and/or clinical courses may be clues leading to diagnosis: (C)
   (i) Fulminant-type infection with GAS: abdominal pains and a non-reassuring fetal status suggestive of placental abruption following flu-like symptoms.
   (ii) Fulminant type I diabetes mellitus: flu-like symptoms following thirst, polydipsia, and polyuria lasting for several days.
   (iii) Aorta dissection: excruciating chest or back pain occurring abruptly during the late stage of pregnancy or peripartum.
   (iv) Long QT syndrome: sudden arrhythmia and syncope.
   (v) Pulmonary thromboembolism: sudden dyspnea and/or chest pain occurring post-partum.
   (vi) Amniotic fluid embolism: cardiopulmonary collapse occurring abruptly at the time of fetal membranes rupture or soon after delivery.
   (vii) Peripartum cardiomyopathy: dyspnea, orthopnea, cough, and edema occurring during the late stage of pregnancy and within 6 months after delivery

Chapter G. Infection

CQ601: How should pregnant women with bacterial vaginosis (BV) be treated?
Answer

1 Treat women with symptomatic BV. (B)
2 Provide a test for the detection of BV in women with a risk factor for preterm birth, such as a history of preterm birth. (C)
3 Treat women with BV and a risk for preterm birth, such as a history of preterm birth, using antibiotics. (C)

CQ602: How should pregnant women with urogenital *Chlamydia trachomatis* infections be treated?
Answer

1 Provide a test for the detection of *C. trachomatis* for the prevention of neonatal *C. trachomatis* infection. (B)
2 Diagnose urogenital *C. trachomatis* infection when *C. trachomatis* is detected using nucleic acid amplification tests, nucleic acid hybridization tests, an enzyme immunoassay, or culture methods in specimens obtained from the uterine cervix. (B)
3 Treat with a single dose of oral azithromycin (1.0 g) or oral clarithromycin (200 mg × 2/day, 7 days). (B)
4 Recommend that the partner of any woman infected with *C. trachomatis* undergo a screening test for *C. trachomatis* infection. (C)

CQ603: How should women with genitourinary group B streptococcal (GBS) infection be treated?

Answer

1 Obtain a specimen for GBS cultivation at a gestational term of 33–37 weeks. (B)
2 Obtain specimens from the introitus of both the vagina and the anus. (C)
3 Administer penicillin/ampicillin i.v. to women with any of the following characteristics to prevent early-onset GBS diseases of the infant during labor or after premature membrane rupture: (B)
   (i) GBS infection in a previous infant (even in the absence of GBS in the current pregnancy).
   (ii) A positive GBS result except in women undergoing an elective cesarean section.
   (iii) Incidental detection of GBS in a urine culture during the current pregnancy
   (iv) Women with an unknown GBS status and any of the following conditions:
      • Preterm delivery (gestational age <37 weeks).
      • Eighteen hours or longer after fetal membranes rupture.
      • Febrile condition (>38°C).
4 Administer antibiotics for 3 days to eradicate GBS in women with continued premature membrane rupture. (C)

CQ604: How should pregnant women with antibodies against toxoplasma be treated?

Answer

1 Provide information to all pregnant women regarding appropriate behaviors to prevent toxoplasma infection. (C)
2 Estimate the timing of the toxoplasma infection using specific IgG and IgM antibodies against toxoplasma. (B)
3 Remember that a positive IgM antibody status does not necessarily indicate a recent infection occurring within several months, as the phenomenon of 'persistent IgM,' in which positive IgM antibodies sometimes persist for a long time (≥3 months), has been known to occur. Carefully treat women with a positive IgM status for toxoplasma. (B)
4 Administer oral acetylspiramycin to women infected after the establishment of the current pregnancy. (B)
5 Consider the administration of pyrimethamine and sulphadiazine at between 16 and 27 gestational weeks in women with a suspected fetal infection (see Discussion). (C)

CQ605: How should women with rubella infection during pregnancy be treated?

Answer

1 Screen all women to detect patients with rubella infection during an early stage of pregnancy using HI (titer of antibody against rubella). (A)
2 Obtain the following information from women during an early stage of pregnancy: (B)
   (i) Occupation during the past 3 months.
   (ii) Contact with rubella patients during the past 3 months.
   (iii) Skin rash during the past 3 months.
   (iv) Febrile disease during the past 3 months.
   (v) Swelling of cervical lymph nodes during the past 3 months.
3 Take diagnostic measures in women with any of the following findings:
   (i) Contact with rubella patients. (B)
   (ii) Symptoms suggestive of rubella infection, such as skin rash, febrile condition, and swollen lymph nodes. (B)
   (iii) Titer of antibody (HI) ≥ × 256 during early pregnancy. (C)
4 Remember that diagnostic measures should include both repeated measures of the HI titer in paired sera samples and measures of specific IgM antibody. (B)
5 Administer vaccine to post-partum women with an HI antibody titer ≤ × 16. (C)
6 When a client is suspected of having a rubella infection during pregnancy, examine the cord blood and specimens from the throat and/or saliva of the neonate to enable a diagnosis of congenital rubella infection. (C)
7 Consult a regional health center regarding diagnostic measures for 'congenital rubella syndrome (CRS)' if necessary and report the CRS case to the regional health center if a diagnosis is made. (A)

CQ606: How should women with HBs-antigen be treated?

Answer

1 Do not report a positive test result for HBs antigen to family members before obtaining the permission of the woman with the positive HBs-antigen test result. (B)
2 Determine the status of HBe-antigen and liver function and tell women about the risk of HBV vertical transmission. (A)
3 Recommend a visit to an appropriate physician. (C)

4 Take measures including the administrations of HB immunoglobulin and vaccination against HBV to prevent HBV vertical transmission, in cooperation with pediatricians. (A)
5 Tell women that breast-feeding does not increase the risk of HBV vertical transmission, providing that preventive measures are being taken. (B)

CQ607: How should women with HCV-antibody be treated?

Answer

1 Do not report a positive test result for HCV antibody to family members before obtaining the permission of the woman with the positive HCV antibody test result. (B)
2 Quantify HCV-RNA in the blood and examine liver function. (A)
3 Tell women with undetectable HCV-RNA that HCV vertical transmission does not occur. (B)
4 Tell women with detectable HCV-RNA that there may be a risk of HCV vertical transmission. (B)
5 Recommend that women with detectable HCV-RNA visit appropriate physicians. (C)
6 Tell women with detectable HCV-RNA that vertical transmission via breast-milk does not occur.
7 Provide information on the Japanese vertical transmission rates according to titers of HCV-RNA and delivery modes in women with a higher HCV-RNA. Help women to choose a delivery mode according to these data. (C)

CQ608: How should pregnant women with genital herpes be treated?

Answer

1 During the first trimester, apply acyclovir ointment to the lesions and advise the patient to refrain from sexual activities. (B)
2 During the second or third trimester, administer systemic anti-viral drugs to women with a primary infection or first-episode disease. (B)
3 Recommend an elective cesarean section in women with any of the following statuses:
   (i) Presence of genital lesions at supposed time when labor will occur. (A)
   (ii) Labor pains occurring within 4 weeks of the manifestation of the primary infection. (C)
   (iii) Labor pains occurring within 1 week of the manifestation of a recurrence or non-primary first-episode disease. (C)
4 Pay attention to the neonate with respect to symptoms derived from congenital infection. (B)

CQ609: How should women with cytomegalovirus (CMV) infection be treated?

Answer

1 Note that women with a negative CMV IgG status are at a high risk of primary CMV infection during pregnancy. (B)
2 Explain measures for preventing CMV infection to women with a negative CMV IgG status. (C)
3 Interpret the results of maternal CMV-antibody as follows: (B)
   (i) Diagnose as primary infection during pregnancy when seroconversion (change from a negative CMV-IgG during early pregnancy to a positive CMV-IgG during pregnancy) is observed.
   (ii) The effects of CMV on the fetuses are milder in women who acquired CMV before pregnancy (a positive CMV-IgG during early pregnancy), compared with those of a primary infection during pregnancy, although adverse effects on the fetuses may occur.
   (iii) Consider recent infection in women with a positive CMV-IgM, but be cautious of persistent CMV-IgM (the phenomenon of long-lasting IgM positivity).
4 Consider that fetuses with growth restriction, enlarged cerebral ventricle, microcephalus, a high-echoic periventricular area, ascites, and/or hepatosplenomegaly may be infected with CMV. (C)
5 When asked, inform women that no helpful fetal therapy has been established. (B)
6 Remember that infected fetuses are likely to have an abnormal fetal heart rate pattern during labor. (C)
7 Diagnose as congenital infection when CMV-IgM is detected in the cord blood and/or CMV is detected in the urine of neonates within 2 weeks after birth. (A)
8 Refer infants with congenital infection to an appropriate physician for the long-term follow-up of development and auditory function. (A)

CQ610: How should women with HIV infection be treated?

Answer

1 Screen all women for the detection of patients with HIV infection early during pregnancy using tests for HIV screening. (A)
2 In cases with a positive screening test result, do the following: (A)

(i) Inform the woman that 19 out of 20 women with a positive screening test result are not actually infected.
(ii) Perform a Western blotting test and a nucleic acid amplification test simultaneously to confirm the screening result.

3 Consult with a regional designated hospital regarding patients with HIV/AIDS. (C)
4 Perform all of the following measures to prevent vertical transmission: (B)
(i) Treat infected women with antiretroviral drugs during pregnancy.
(ii) Elective cesarean delivery.
(iii) Formula milk feeding.
(iv) Prophylactic administration of antiretroviral drugs to the neonate.

CQ611: How should pregnant women with varicella infection be treated?

Answer

1 Do not administer varicella vaccine to pregnant women. (A)
2 Tell women as follows when asked about varicella infection during pregnancy: (B)
(i) Congenital varicella syndrome is reportedly seen in 0.55%, 1.4%, and 0.0% of neonates born to mothers infected with varicella during the first, second, and third trimesters of their pregnancies, respectively.
(ii) No infants with congenital varicella syndrome and/or malformation as a result of varicella infection have been born to mothers in whom an erroneous vaccination was administered during the 3 months prior to the establishment of pregnancy or during pregnancy.
(iii) Women with neither a history of varicella infection nor vaccination against varicella should refrain from contact with patients with varicella.
3 Administer prophylactic i.v. gammaglobulin (2.5–5.0 g) to women who have been in close contact with a patient infected with varicella during the previous 2 weeks and who may be susceptible to varicella infection because of a possible lack of antibody. (C)
4 Administer acyclovir to pregnant women with varicella infection to prevent serious complications. (C)
5 Treat the mother and neonate as follows when the mother manifests a varicella infection during the 5 days prior to delivery or 2 days post-partum: (B)
(i) Administer acyclovir to the mother.
(ii) Administer i.v. gammaglobulin to the neonate.
(iii) Administer acyclovir to neonates with symptoms of varicella infection.
6 Isolate in-hospital pregnant women with varicella infection in a private room away from other women to prevent in-hospital horizontal transmission. (C)

CQ612: How should women with a positive screening test result for HTLV-1 infection be treated?

Answer

1 Note that a considerable number of women show a false-positive result on screening tests for HTLV-1 infection (particle agglutination or enzyme linked immunosorbent assay). (A)
2 Diagnosis as an HTLV-1 carrier only after a confirmation test (Western blot analysis) shows a positive result. (A)
3 Inform women of their diagnosis as an HTLV-1 carrier very carefully, with consideration of ethical problems. (A)
4 Inform the patient's family of their diagnosis as an HTLV-1 carrier only after receiving the patient's permission. (B)
5 Instruct the patient in the following methods as alternatives to breast-feeding for the prevention of HTLV-1 vertical transmission: (B)
(i) Formula feeding.
(ii) Frozen-thawed breast milk.
(iii) Short-term breast-feeding within the first 3 months after birth.

CQ613: How should women with syphilis be treated?

Answer

1 Screen all women for the detection of patients with syphilis using two methods (a non-specific test and a specific test for *Treponema pallidum*). (A)
(i) Non-specific tests include serological tests for syphilis (STS), such as an agglutination test, VDRL test, or RPR card test.
(ii) Specific tests include FTA-ABS and TPHA.
2 Promptly administer antibiotics, such as penicillin, to women with active syphilis. (A)
3 Assess the effect of treatment at 28–32 weeks of gestation and perinatally using the STS titer. (C)
4 Assess the fetus during the latter half of the pregnancy with respect to signs of infection, such as hepatomegaly, ascites, hydrops, and a thickened placenta, in infected women. (C)
5 Examine the neonate born to an infected mother with respect to congenital syphilis, according to Table 2. (A)

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6 Remember that physicians must notify the regional public health center within 7 days of diagnosing a new patient with syphilis. (A)

CQ614: How should women with parvovirus B19 (PB19) infection be treated?

Answer

1 Remember the following two points: (B)
   (i) Co-living with a patient with PB19 infection is a risk factor.
   (ii) Flu-like symptoms associated with erythema and arthralgia are signs of a PB19 infection.
2 Determine the anti-PB19 IgM titer if a PB19 infection is suspected. (B)
3 Assess fetal anemia and hydrops in cases with maternal PB19 infection, as approximately 10% of such fetuses develop anemia, hydrops and/or die. (C)
4 Consider PB19 infection as a differential diagnosis for fetal hydrops. (B)
5 Recommend that infected women wash their hands and wear a flu mask to prevent in-hospital horizontal transmission. (C)
6 Remember that the following facts are known about PB infection during pregnancy: (C)
   (i) Ninety percent of hydrops fetalis cases develop within 8 weeks (median, 3 weeks) after maternal infection with PB19.
   (ii) Fetal mortality is higher for maternal infection at <20 weeks of gestation than for maternal infection at >20 weeks.
   (iii) Spontaneous remission occurs in one-third of hydrops fetalis cases.
   (iv) A blood transfusion to the fetus may be effective for improving the outcome.
   (v) The outcome of the surviving fetuses with PB19 infection is similar to that of non-infected fetuses.
   (vi) There is no animal or environmental reservoir and humans are critical to maintaining transmission.

Chapter H. Twin Pregnancies

Q701: How should chorionicity be determined for a twin pregnancy?

Answer

1 Determine chorionicity until the end of 10 weeks of gestation. (A)
2 Count the numbers of chorions and amnions using ultrasonography to determine the chorionicity and amnionicity. (A)
   (i) Diagnose as monochorionic and dichorionic twins in cases with one and two gestational sacs (GS), respectively, as the number of GS equals that of the chorion.
   (ii) Diagnose as dichorionic in cases with a relatively thick dividing membrane (inter-twin septum).
   (iii) Diagnose as diamniotic in cases of monochorionic twins with a thin dividing membrane.
   (iv) Presume monochorionic monoamniotic twins and repeat the ultrasonography examination in cases with an unrecognizable dividing membrane.
3 Determine the chorionicity and amnionicity referring to the presence or absence of a twin peak sign, the number of placentas, and the fetal sex in cases with undetermined chorionicity at ≥14 weeks of gestation. (B)

Q702: How should women with monochorionic twin pregnancies be treated?

Answer

1 Refer women to secondary or tertiary institutions or treat the women in cooperation with those institutions. (B)
2 Provide information on the risks associated with monochorionic twins. Be cautious of the occurrence of twin-to-twin transfusion syndrome and twin reversed arterial perfusion sequence. (B)
3 Determine amnionicity (mono- or di-) before 14 weeks of gestation. (B)
4 Examine using ultrasonography at least once every 2 weeks in cases with diamniotic twin pregnancy, paying attention to discordances in volumes of the amniotic fluid and/or fetal development. (C)
5 Provide information on the risk of sudden fetal death as a result of cord entanglement in women with monoamniotic twins. (C)

Q703: How may twin-to-twin transfusion syndrome (TTTS) and a twin reversed arterial perfusion (TRAP) sequence be detected in monochorionic pregnancy?

Answer

1 Presume TTTS and examine extensively in a case with a tendency toward polyhydramnios in one twin and oligohydramnios in the co-twin. (B)
2 Presume a TRAP sequence and examine extensively when a dead twin is growing. (B)

Q704: How should women with twin pregnancies and a single fetal death be treated?

Answer

1 Manage expectantly, but pay attention to maternal DIC in dichorionic twin pregnancies. (B)
2 Manage expectantly, but pay attention to anemia and the well-being of the surviving twin in monochorionic twin pregnancies. (C)
3 Inform women with a monochorionic placenta that the surviving twin is at an extraordinarily high risk of developing permanent disabilities or perinatal mortality, even with the best of treatment. (C)

CQ705: What general cautions are needed when managing women with twin pregnancies?

Answer

1 Pay attention to clinical signs of preterm labor during the latter half of pregnancy. (A)
2 Perform blood tests, including platelet count and antithrombin activity, at and after gestational week 33, as pregnancy-induced hypertension, HELLP syndrome, and venous thromboembolism are more likely to occur during the late stage of pregnancy. (C)
3 Pay closer attention to fetal well-being at ≥37 weeks of gestation in twin pregnancies than in singleton pregnancies. (B)
4 Refer to the following when choosing a delivery mode: (C)
   (i) Both twins are cephalic presentation: vaginal delivery
   (ii) First twin is cephalic and the second twin is non-cephalic: similar cautions to those for the vaginal delivery of a singleton with a breech presentation are required during the vaginal delivery trial (see CQ402).
   (iii) First twin is non-cephalic presentation: elective cesarean section.
5 Monitor the fetal heart rate (FHR) patterns of both fetuses continuously and simultaneously during labor. (B)
6 Confirm the fetal position and FHR pattern of the second twin immediately after the vaginal birth of the first twin. (B)
7 Pay attention to post-partum hemorrhage and peripartum venous thromboembolism. (C)

Chapter I. Newborns

CQ801: How should neonates with birth asphyxia be resuscitated?

Answer

1 Physicians, midwives and nurses are required to make every effort to acquire knowledge and the necessary skills to perform neonatal resuscitation, as one in 100 neonates requires resuscitation immediately after birth. (A)
2 Assess the following three points immediately after birth: (A)
   (i) Not an immature infant.
   (ii) Good breathing/crying.
   (iii) Good muscle tone.
3 Care for neonates routinely, as shown in Table 1, in cases meeting all three conditions described in Answer 2. (B)
4 Perform the 'primary resuscitative procedures' outlined in Table 2 if any abnormality is present among the three conditions shown in Answer 2. (B)
5 Take further resuscitative measures in cases in which 'primary resuscitative procedures' have failed, referring to Figure 1 posted on the wall of the delivery room. (C)
6 Determine the Apgar scores at 1 and 5 min and record the values. (B)
7 Analyze the umbilical arterial blood gas and record the findings. (C)
8 Be cautious of maintaining an adequate neonatal body temperature. (B)
9 Consult neonatologists or experienced physicians if there is any concern regarding the neonate's condition. (B)
10 Provide 'Early skin-to-skin contact,' referring to the Guidelines, after obtaining informed consent regarding 'Early skin-to-skin contact.' (C)

CQ802: How should newborns be cared for within 10 days after birth?

Answer

1 Apply eye drops or ointment containing antibiotics to the eyes of newborns to prevent conjunctivitis. (B)
2 Confirm the absence of congenital anomalies, birth injuries, extremity paralysis and cephalohematoma, etc. (B)
3 Regularly assess body temperature, bodyweight, respiration, feeding conditions, activities, and skin color (jaundice and cyanosis). (B)
4 Remember that clinical impressions, such as a lack of vigor, bad skin color, or tachypnea, are often clues for the diagnosis of specific abnormalities in newborns. (B)
5 Suspect a possible infection, hypoglycemia, congenital heart disease, gastrointestinal disease,

hemolytic disease, or congenital metabolic disease if a neonate exhibits any of the abnormalities described in Answer 5. (B)
6 Administer vitamin K to neonates in an adequate manner (refer to the Discussion). (B)
7 Provide mass-screening tests for the detection of congenital metabolic diseases and an auditory test for neonates after obtaining the parents' informed consent. Record the results in the 'Booklet for mother and child,' known in Japanese as *boshitecho*. (C)
8 Provide information regarding congenital biliary tract obstruction, with reference to photos showing various colors of neonatal stool printed in the *boshitecho*, for the early detection of congenital biliary tract obstruction. (C)
9 Remember that discharge from the hospital within 3 days after birth is associated with an increased risk of re-hospitalization for jaundice and/or dehydration. (C)
10 Keep in contact with regional public health nurses or city officers who may be concerned with neonatal health, if necessary. Confirm the developmental status of neonates at 1–2 weeks after their discharge from hospital. (C)
11 Support mothers to establish breast-feeding. (C)
12 Pay attention to the safe preparation and preservation of formula milk, referring to Table 2. (B)

CQ803: How should late preterm infants (born at gestational week 34, 35, and 36) be treated?
Answer

1 Perform 'primary resuscitative procedures' (See CQ801). (B)
2 Measure the blood glucose level, as late preterm infants are prone to hypoglycemia. (C)
3 Monitor the respiration status, as late preterm infants are prone to apnea. (C)
4 Provide the following information on respiratory syncytial virus (RSV) infection to women with delivery at gestational week 34 or 35: (C)
- RSV infection is likely to develop into severe complications.
- The prophylactic administration of certain drugs to preterm infants during RSV season prevents or reduces severe complications caused by RSV.
- Provide a list of clinics at which drugs for RSV prophylaxis are available.

CQ804: How should the cause of intrauterine fetal death (IUFD) at ≥22 weeks of gestation be determined and how should women with IUFD be treated?
Answer

1 Estimate the time of IUFD in an integrated manner. (A)
2 Determine the cause of death using the following tests:
Fetal factors
(i) Macroscopic inspection of the stillborn infant, placenta and the umbilical cord. (A)
(ii) Histopathological examination of the placenta and umbilical cord. (C)
(iii) Autopsy of the stillborn infant. (C)
(iv) X-ray examination of the whole body of the stillborn infant, or equivalent examinations. (C)
(v) Chromosomal analysis. (C)
Maternal factors
(vi) Tests such as the indirect Coombs test for atypical antibodies against erythrocytes in cases with an undetermined antibody status. (B)
(vii) Tests for antiphospholipid antibody, including lupus anticoagulant, anti-cardiolipin antibody, and anti-cardiolipin β2GP1 antibody. (C)
(viii) Tests for syphilis in undetermined cases.
(ix) Tests for parvovirus B19 or other TORCH infections. (C)
(x) Tests for glucose tolerance and thyroid function. (C)
(xi) Tests for coagulation-fibrinolysis system. (C)
(xii) Test for fetomaternal transfusion. (C)
3 Provide information regarding the risk of recurrence in siblings of IUFD cases with structural malformations and/or chromosomal aberrations at the request of the mother/family. (B)
4 Support the mother and family psychologically and emotionally with counseling and other forms of assistance. (B)

Chapter J. Others

CQ901: How should one respond when asked about the effects of car seatbelts during pregnancy and the effects of child car seats?
Answer

1 Explain as follows: (A)
(i) Damage from car accidents is reduced if seatbelts are applied in an appropriate manner. The chest belt should pass between the breasts, and

the waist belt should pass below the pubic bone; neither belt should cross the protruding abdomen.
(ii) The correct application of child car seats is especially important to reduce injuries to infants as a result of car accidents.

CQ902: How should female patients involved in multiple casualty incidents be treated?
Answer

1 Consider the possibility of a casualty being pregnant while performing triage and while treating and transporting female casualties. (B)
2 Tag pregnant patients with a yellow card and those with a rupture of fetal membranes, genital bleeding, pain in the abdomen, and/or fetal death with a red card during primary triage. (C)
3 Support mothers to continue breast-feeding. (B)
4 Establish a regional network for communication and the roles of individuals in a community as preparation for future large-scale disasters. (C)

CQ903-1: How should pregnant women with a sudden (impending) cardiac arrest be treated?
Answer

1 Perform the following measures in women with an impending cardiac arrest: (C)
   (i) Gather medical staff.
   (ii) Perform manual left displacement: displace the uterus to the patient's left or place the patient in a full left-lateral position to relieve possible compression of the inferior vena cava.
   (iii) Provide 100% oxygen.
   (iv) Establish i.v. access above the diaphragm.
   (v) Consider reversible causes of critical illness and treat conditions that may contribute to clinical deterioration as early as possible.
2 Perform the following resuscitative measures in women with cardiac arrest: (C)
   (i) Gather medical staff.
   (ii) Perform manual left displacement: displace the uterus to the patient's left or place the patient in a full left-lateral position to relieve possible compression of the inferior vena cava.
   (iii) Start chest compressions. Place hands slightly higher on the sternum than usual.
   (iv) Ventilate with 100% oxygen.
   (v) Do not delay defibrillation with an AED.
   (vi) Administer adrenalin via a venous line.
   (vii) Perform a perimortem cesarean when patients are unresponsive to the measures described above.

CQ903-2: How should one behave after experiencing an incidental maternal mortality?
Answer

1 Notify the 'accident investigation committee' of each hospital. (A)
2 Contact the central and prefectural offices of the Japan Association of Obstetricians & Gynecologists (JSOG) and report the incident in detail. (A)
3 Make every effort to obtain consent to perform an autopsy. (A)

Disclosure

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総説

妊産婦等における適正使用情報の収集・活用の現状と問題点 —SEA分類と「使用上の注意」への記載について—

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Current Situations and Issues of Collection and Practical Use of Information for Proper Use of Drugs in Expectant and Nursing Mothers —SEA Pregnancy Category and its Application to "Precautions" in Medical Package Insert—

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1. はじめに

妊娠期あるいは授乳期の女性における医薬品の適正使用情報に関する最大の問題は，その医薬品の開発段階での様々な情報収集が難しいこと等の理由により，医薬品添付文書の記載が十分とはいえないことである．そのため，臨床現場において誤解や混乱が生じることもあり，結果的にそうした女性やその胎児・出生児が不利益を被る可能性がある．

この問題の解決のための試みはいくつかなされているが，我々は厚生労働科学研究費補助金による研究事業として，妊娠期の女性に対する医薬品使用に関連したSEA分類と称するリスク分類を構築，提唱している[1]．

本稿では，まずリスク分類について述べ，次いでこのSEA分類と本分類の医薬品添付文書の「使用上の注意」への記載について紹介したい．

2. リスク分類とは

わが国には存在しないが，諸外国には妊娠中の医薬品使用に伴う胎児危険度を表すリスク分類（公的リスクカテゴリー）が存在する．妊娠女性における医薬品の適正使用情報を臨床現場に届ける一つの手段として用いられている．主として，その医薬品による催奇形性を中心とした胎児へのリスクの観点から医薬品を分類するものである．

2.1 FDA分類とオーストラリア分類

そうした既存のリスク分類の中で最も有名なのは，米国食品医薬品局（FDA: Food and Drug Administration）から発表されている，いわゆるFDA分類である（Table 1）．米国の従来からの医薬品添付文書にはPregnancy Categoryとして記載されている[2]．その特徴としては，ヒトあるいは動物における研究結果を重視した分類であることがあげられる．主として研究で得られた証拠を吟味して医薬品を分類するように作成されている．

次いで有名なのは，オーストラリア医薬品評価委員会（Australian Drug Evaluation Committee: ADEC）から発表されている，いわゆるオーストラリア分類[3]である（なお，ADECは2010年1月より後継機関である処方箋医薬品諮問委員会（Advisory Committee on Prescription Medicines: ACPM）にその業務を引き継いでいる）（Table 2）．オーストラリア分類は，ヒトに関するデータとして過去の妊娠女性での臨床使用経験を重視している分類であり，臨床医にはFDA分類より使用しやすいともいわれている．

2.2 従来のリスク分類の問題点

FDA分類やオーストラリア分類などのリスク分類については，わが国でも長い間汎用されてきた．特に，記号化

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Table 1　FDA 分類

A:	Controlled studies in women fail to demonstrate a risk to the fetus in the first trimester (and there is no evidence of a risk in later trimesters), and the possibility of fetal harm appears remote. ヒトの妊娠第一三半期の対照試験で，胎児への危険性は証明されず，またその後の妊娠期間でも危険であるという証拠もなく，胎児への障害の可能性が低いもの．
B:	Either animal-reproduction studies have not demonstrated a fetal risk but there are no controlled studies in pregnant women, or animal-reproduction studies have shown an adverse effect (other than a decrease in fertility) that was not confirmed in controlled studies in women in the first trimester (and there is no evidence of a risk in later trimesters). 動物生殖試験では胎仔への危険性は否定されているが，ヒト妊婦での対照試験は実施されていないもの．あるいは，動物生殖試験で有害な作用（または出生数の低下）が証明されているが，ヒトでの妊娠第一三半期の対照試験では実証されていない，またその後の妊娠期間でも危険であるという証拠はないもの．
C:	Either studies in animals have revealed adverse effects on the fetus (teratogenic or embryocidal or other) and there are no controlled studies in women, or studies in women and animals are not available. Drugs should be given only if the potential benefit justifies the potential risk to the fetus. 動物生殖試験では胎仔に催奇形性，胎仔毒性，その他の有害作用があることが証明されており，ヒトでの対照試験が実施されていないもの．あるいは，ヒト，動物ともに試験は実施されていないもの．ここに分類される薬剤は，潜在的な利益が胎児への潜在的危険性よりも大きい場合にのみ使用すること．
D:	There is positive evidence of human fetal risk, but the benefits from use in pregnant women may be acceptable despite the risk (e.g., if the drug is needed in a life-threatening situation or for a serious disease for which safer drugs cannot be used or are ineffective). ヒトの胎児に明らかに危険であるという証拠があるが，危険であっても，妊婦への使用による利益が容認されるもの（例えば，生命が危険にさらされているとき，または重篤な疾病で安全な薬剤が使用できないとき，あるいは効果がないとき，その薬剤をどうしても使用する必要がある場合）．
X:	Studies in animals or human beings have demonstrated fetal abnormalities, or there is evidence of fetal risk based on human experience or both, and the risk of the use of the drug in pregnant women clearly outweighs any possible benefit. The drug is contraindicated in women who are or may become pregnant. 動物またはヒトでの試験で胎児異常が証明されている場合，あるいはヒトでの使用経験上胎児への危険性の証拠がある場合，またはその両方の場合で，この薬剤を妊婦に使用することは，他のどんな利益よりも明らかに危険性の方が大きいもの．ここに分類される薬剤は，妊婦または妊娠する可能性のある婦人には禁忌である．

されていて単純に理解しやすいことが，多くの医師に受け入れられてきた理由である．しかしながら，近年こうしたリスク分類についてその問題点が指摘されるようになってきた．

まず，FDA 分類が重視するヒトあるいは動物における研究結果も，オーストラリア分類が重視する過去の臨床使用経験も，妊娠女性における適正使用情報としてはどちらも等しく重要なのではないかという指摘である．そうしたバランスがとれたリスク分類は未だ存在しない．また，その医薬品がなぜそのカテゴリーに入ると判定されるのかの根拠（元となる情報・エビデンス）が伝わらず，同じカテゴリーに全く異なる理由から分類された様々な医薬品が含まれてしまっており，同じカテゴリーの医薬品でもリスクの大きさとしてはまったく一定ではない，との批判もある．

更に，あくまで分類であり，A から X にかけてリスクが上昇するような順位づけをしたものではないにもかかわらず，アルファベットのみが一人歩きして，あたかも A ～ X にかけて胎児への危険度が増すものと誤解され，一人歩きしてしまっている点も問題点としてあげられている．加えて，特に FDA 分類は臨床的対応の目安となりにくいことも指摘されている．

2.3　問題点の改善の動き

こうした指摘や批判を受けて 2008 年，FDA は，個々の医薬品について記号化による分類を廃止し，一定の項目を文章で記述する新しい形式を提案することとなった[4]．現在，各医薬品について少しずつこうした記述がまとめられている．一方，オーストラリア分類については形式の変更予定はないものの，ACPM は A から X にかけてリスクが上昇するような順位づけをしたものではないことなどの注意点を強調している．

こうした改善の動きは，もちろん妊娠女性に対して医薬品が適正に使用されることを目的としたものではあるものの，従来のリスク分類の問題点をすべて解決するものではない．有用性も高く評価されてきた FDA 分類の廃止という結論になったこともあり，我々は新たなリスク分類の構築を目指し，検討を開始した．

3.　新しいリスク分類の構築に向けて

新しいリスク分類の構築に向けて，我々が目標としたものは以下のような分類である．

第一に，従来のリスク分類と比較して，その医薬品がそのカテゴリーに分類された根拠情報（ヒトでの研究成果，

Table 2 オーストラリア分類

A:	Drugs which have been taken by a large number of pregnant women and women of childbearing age without any proven increase in the frequency of malformations or other direct or indirect harmful effects on the fetus having been observed. 多数の妊婦および妊娠可能年齢の女性に使用されてきた薬だが，それによって奇形の頻度や胎児に対する直接・間接の有害作用の頻度が増大するといういかなる証拠も観察されていない．
B1:	Drugs which have been taken by only a limited number of pregnant women and women of childbearing age, without an increase in the frequency of malformation or other direct or indirect harmful effects on the human fetus having been observed. Studies in animals have not shown evidence of an increased occurrence of fetal damage. 妊婦および妊娠可能年齢の女性への使用経験はまだ限られているが，この薬による奇形やヒト胎児への直接・間接的有害作用の発生頻度増加は観察されていない．動物を用いた研究では，胎仔への障害の発生が増加したという証拠は示されていない．
B2:	Drugs which have been taken by only a limited number of pregnant women and women of childbearing age, without an increase in the frequency of malformation or other direct or indirect harmful effects on the human fetus having been observed. Studies in animals are inadequate or may be lacking, but available data show no evidence of an increased occurrence of fetal damage. 妊婦および妊娠可能年齢の女性への使用経験はまだ限られているが，この薬による奇形やヒト胎児への直接・間接的有害作用の発生頻度増加は観察されていない．動物を用いた研究は不十分または欠如しているが，入手しうるデータでは，胎仔への障害の発生が増加したという証拠は示されていない．
B3:	Drugs which have been taken by only a limited number of pregnant women and women of childbearing age, without an increase in the frequency of malformation or other direct or indirect harmful effects on the human fetus having been observed. Studies in animals have shown evidence of an increased occurrence of fetal damage, the significance of which is considered uncertain in humans. 妊婦および妊娠可能年齢の女性への使用経験はまだ限られているが，この薬による奇形やヒト胎児への直接・間接的有害作用の発生頻度増加は観察されていない．動物を用いた研究では，胎児への障害の発生が増えるという証拠が得られている．しかし，このことがヒトに関してどのような意義をもつかは不明である．
C:	Drugs which, owing to their pharmacological effects, have caused or may be suspected of causing, harmful effects on the human fetus or neonate without causing malformations. These effects may be reversible. Accompanying texts should be consulted for further details. 催奇形性はないが，その薬理効果によって，胎児や新生児に有害作用を引き起こし，または，有害作用を引き起こすことが疑われる薬．これらの効果は可逆的なこともある．詳細は付記した本文を参照のこと．
D:	Drugs which have caused, are suspected to have caused or may be expected to cause, an increased incidence of human fetal malformations or irreversible damage. These drugs may also have adverse pharmacological effects. Accompanying texts should be consulted for further details. ヒト胎児の奇形や不可逆的な障害の発生頻度を増す，または，増すと疑われる，またはその原因と推測される薬．これらの薬にはまた，有害な薬理作用があるかもしれない．詳細は付記した本文を参照のこと．
X:	Drugs which have such a high risk of causing permanent damage to the fetus that they should not be used in pregnancy or when there is a possibility of pregnancy. 胎児に永久的な障害を引き起こすリスクの高い薬であり，妊娠中あるいは妊娠の可能性がある場合は使用すべきでない．

妊娠女性での臨床使用経験，動物実験データ）がより理解しやすい分類である．根拠情報の質や量は，医薬品によって大きく異なるが，その質や量を知ることは使用者である医師，薬剤師にとってきわめて重要である．ただし，そのためにFDAの新しい方針のように，記号化による分類を廃止し一定の項目を文章で記述する形式にすることは，今度は記号化されることのメリットがなくなるため，ある程度「5段階程度のランク」としてとらえやすい分類が望ましいのではないかと考えた．なおかつ，臨床的対応の目安となる分類を目標とした．妊娠女性，あるいは妊娠の可能性のある女性に対して，医師が医薬品使用を検討した際に役立ってこそ，リスク分類としての意義があるからである．更に，理想的には医薬品添付文書の「使用上の注意」への展開を視野に入れた分類がよいのではないかと考えた．

上述したように，妊娠女性やその胎児に対する医薬品の影響を考えるときに根拠となる情報は主に以下の三つである．

○ヒトにおける研究成果（Study）
○妊娠女性での臨床使用経験（Experience）
○動物実験データ（Animal experiment）

そのそれぞれについて何段階かに分類して，それをまとめて表記する分類が，根拠情報がある程度理解でき，かつ記号化のメリットを残す，臨床的にも有用なよりよい分類になるのではないか，との結論に達した．そして，その根拠情報三つの頭文字をとって「SEA 分類」と称することにした．

4. SEA 分類

SEA 分類は，ヒトにおける研究成果のみから分類するS分類，妊娠女性での臨床使用経験のみから分類するE分類，動物実験データのみから分類するA分類に分かれて

おり，それら三つの分類結果からリスクグレード(G)を決定するという構成になっている．更に，実際の臨床現場では，妊娠女性に対してはより安全で代替可能な医薬品の有無等を考慮して臨床的対応を決定するため，そうしたいわば有益性や実利(Utility：U)を加味することが大切であり，その上での総合評価を明示することで，臨床的有用性の高いリスク分類となっている．

4.1 S 分類：ヒトにおける研究成果

SEA 分類のうち，ヒトにおける研究成果を元にしたS分類について，Table 3 に示した．このS分類の特徴は，ヒトにおける研究成果として，その研究をエビデンスレベルに応じて明確に区別していることにある．研究を大規模比較対照研究とその他の研究に分けるとともに，それぞれを定義している．このため，その医薬品がヒトにおいて催奇形性や胎児毒性が認められているのか，認められているとすればどのエビデンスレベルでの研究成果なのか，がS分類の数字を見るだけである程度わかる分類となっている．

4.2 E 分類：妊娠女性での臨床使用経験

SEA 分類のうち，妊娠女性での臨床使用経験を元にしたE分類について，Table 4 に示した．この臨床使用経験をどのように評価して分類を行うかが，この分類での最大

Table 3　S 分類

S0: 大規模比較対照研究#1で催奇形性および胎児毒性のいずれも示されていない．
S1: 他の研究#2で催奇形性および胎児毒性のいずれも示されていない．
S2: 大規模比較対照研究#1または他の研究#2で，軽度・低頻度#3な催奇形性もしくは胎児毒性が示されている．
S3: 大規模比較対照研究#1または他の研究#2で，重度・低頻度または軽度・高頻度#3の催奇形性もしくは胎児毒性が示されている．
S4: 大規模比較対照研究#1または他の研究#2で，重度・高頻度#3の催奇形性もしくは胎児毒性が示されている．
SX: #1，#2を満たす研究がない．

#1：大規模比較対照研究
1) 対照群（プラセボ群，標準薬服用群など matched control）を含めて 300 例以上（当該薬剤服用群 150 例以上）のランダム化比較試験または対照のある前向きコホート研究，あるいはこれらをまとめたメタアナリシス．
2) 類薬 1, 2（別に定義）を含んだ研究でも，当該薬剤として#1 の 1）を満たせば，当該薬剤のみでの解析の有無に関わらず，大規模比較対照研究に含まれる．

#2：他の研究
1) 当該薬剤服用者 50 例以上の研究で，症例対照研究，対照群（matched control）のないコホート研究，調査研究など後ろ向きの研究も含む．
2) 類薬 1, 2 を含んだ研究でも，当該薬剤として#2 の 1）を満たせば，当該薬剤のみでの解析の有無に関わらず，その他の研究に含まれる．
*1：これらの「300」「150」「50」の数字は厳密に遵守する．
*2：#1 および#2 の研究において，薬剤の胎児に対する安全性の評価が主要評価項目（primary endpoint）である必要はない．
*3：#1 や#2 の研究で結論が異なるものがある場合，1)エビデンスレベルの高い方，2) 対象の多い方，3) 新しい方の順に優先して評価し，研究結果を採用する．採用されなかった#1 や#2 の研究はE分類でも用いない．

#3：軽度/重度，低頻度/高頻度
以下のように定義する．
1) 軽度/重度
＜催奇形性に関して＞
軽度：いわゆる「小奇形」か同等以下の先天形態異常
重度：「小奇形」よりも重篤な先天形態異常
＜胎児毒性に関して＞
軽度：致死的でなく，かつ治療により治癒が期待できるもの
重度：致死的または治癒が期待できないもの
2) 低頻度/高頻度
低頻度：有意なリスク上昇がなく，かつ，5%未満の発生
高頻度：有意なリスク上昇があるか，または，5%以上の発生
低頻度，高頻度の両方のデータがある場合，1) エビデンスレベルの高い方，2) 対象の多い方，3) 新しい方の順に優先して採用する．

注1) 授乳期においては，催奇形性は評価せず，機能異常として，胎児毒性の代わりに「新生児毒性」「乳児毒性」を評価する．
注2) 1) 類薬1：同一の薬剤で，投与量，投与期間，投与ルートの違いなどにより，胎児の被曝量（量［血中濃度］×期間）が，標準的投与に比べ，10倍以上多いか少ないと考えられる場合．胎児被曝量がそれ以外か，不明な場合は類薬ではなく，単なる同一薬剤として扱う．
2) 類薬2：薬理学的に類似の作用を持ち，かつ化学構造上類似し，体内動態も類似する薬剤．
3) 類薬3：類薬1，2以外で，薬理学的作用，化学構造のいずれか一方が類似する薬剤．体内動態の類似性は問わない．

Table 4　E 分類

E0: 20 年以上の臨床経験で催奇形性および胎児毒性がどちらも認められていない#3（リスクがあるという症例報告や経験などが知られていない）．妊娠女性に対して日常的によく用いられる#6 薬剤では 10 年以上．
E1: 10 年以上の臨床経験で催奇形性および胎児毒性がどちらも認められていない．妊娠女性に対して日常的によく用いられる薬剤では 5 年以上．または，類薬 1, 2 #4 において 20 年以上の臨床経験で催奇形性および胎児毒性のいずれも認められていない．
E2: 臨床経験で催奇形性もしくは胎児毒性があるが，軽度かつ低頻度#5 である．
E3: 臨床経験で重度・低頻度または軽度・高頻度#5 な催奇形性もしくは胎児毒性が認められている．
E4: 臨床経験で重度かつ高頻度#5 な催奇形性もしくは胎児毒性が認められている．
EX: 臨床経験が 10 年未満の場合で，催奇形性および胎児毒性のいずれも認められていない．妊娠女性に対して日常的によく用いられる#6 薬剤では 5 年未満．

#1：妊娠女性
薬剤投与時に妊娠の診断がされていないが，後に，薬剤投与時に妊娠していたことが判明した女性を含む．
#2：臨床経験
現場での臨床経験と症例報告，症例シリーズなど Study（S 分類）の#1 もしくは #2 に該当しない研究を含む（ただし，当該薬剤を含む研究であり，類薬のみの研究は含まない）．「○年以上」の基準は，原則として国際誕生年からとする．
#3：催奇形性や胎児毒性
催奇形性や胎児毒性が「認められていない」あるいは「ある」は，いずれも一般の背景発現率との比較である．
#4：類薬 1, 2
別に定義する（S 分類参照）．
#5：軽度/重度，低頻度/高頻度
軽度/重度は S 分類と同じ．
低頻度/高頻度は，低頻度：5%未満の発生，高頻度：5%以上の発生，とする．
低頻度，高頻度の両方の報告・経験がある場合，1）対象の多い方，2）新しい方の順に優先して採用する．
#6：妊娠女性に対して日常的によく用いられる
何らかの方法（症例報告，調査など）で，計 200 名以上の投薬と臨床経験が確認されることをさす．

※1：E 分類では，S2-4の場合，S 分類より小さい数値には分類しない（同じはありうる．X にもしない）．ただし，SX の場合，E 分類はすべてあり得る．

の問題であろう．過去の臨床使用経験を重視している上述のオーストラリア分類においても，その評価の方法自体は必ずしも明確ではない．

そこで SEA 分類においては，国際誕生年からの経過年数を基準として，症例報告，症例シリーズなど，S 分類の大規模比較対照研究もしくはその他の研究に該当しない研究を含ませることで，一定の客観性をもたせる工夫を行った．

4.3　A 分類：動物実験データ

SEA 分類のうち，動物実験データを元にした A 分類について，Table 5 に示した．動物実験データは，それをヒトに外挿する際には大きな問題を抱えているものの，こうしてそれ単独で考えた場合には，比較的分類は明瞭であるといえよう．

4.4　SEA 分類によるリスクグレード：G

S, E, A の各分類の結果から，リスクグレード (G) を決定するための一覧表を Table 6 に示した．基本的には S

Table 5　A 分類

A0: 動物実験において，明らかな催奇形性，胚/胎仔/新生仔致死作用，その他の有害作用（変異/骨化遅延，胎仔/新生仔の体重低下，生後の発生指標変化等）が，いずれも認められない．
A1: 動物実験において，明らかな催奇形性および胚/胎仔/新生仔致死作用は認められないものの，その他の有害作用（変異/骨化遅延，胎仔/新生仔の体重低下，生後の発生指標変化等）が認められる．類薬で，A0 または A1 の条件を満たす．
A2: 動物実験において，明らかな催奇形性もしくは胚/胎仔/新生仔致死作用が認められている．類薬での動物実験もこれに含める．
AX: 類薬を含め，適切な動物実験データがない．

※1：母動物毒性量以上，人常用量100倍以上で認められた毒性で，ヒト胎児への影響を直接的に示唆するものではない場合，胎児への影響を過大評価しない．
※2：動物種により結果が異なる場合は，ヒト胎児への影響を直接的に示唆すると判断される場合は A2とし，ヒト胎児への影響を直接的に示唆するものではない場合 A1とする．

Table 6　SEA 分類によるリスクグレード：G

	E0	E1	E2	E3	E4	EX
S0	1	1	1	1	1	1
S1	2	2	3	3	4	-
S2	-	-	3	3	4	-
S3	-	-	-	4	5	-
S4	-	-	-	-	5	-
SX	2	3	3(A0/1) 4(A2)	4	5	3(A0/1) 4(A2)

※1：定義上，S2 E0/1/X A any，S3 E0/1/2/X A any，S4 E0/1/2/3/X A any は存在しない．
※2：SX EX AX は「グレード分類不能」とする．

Table 7　Utility（有益性・実利）：U

U0: より安全な代替可能な薬（G1～3）がない状況があると判断される．
U1: すべての状況で，より安全な代替可能な薬（G1～3）がある．
U2: 不要な薬剤．

Table 8　SEA 分類に Utility を加味した総合評価

A: 児に安全なエビデンスがあり，使用してよい
G1+U0（，G1+U1）
B: 児にほぼ安全といえ，使用してよい
G2+U0
C: 児に一定のリスクはあるが，必要な場合は使用できる
G2+U1，G3+U0/1
D: 特別の状況に限って，使用できる
G4+U0
X: 使用は許容できない
G5+U0，G4/5+U1，G1/2/3/4/5+U2

分類とＥ分類の結果からリスクグレード(G)を決定するが，Ｓ分類において大規模比較対照研究及びその他の研究に該当する研究が全くない場合には，一部Ａ分類の結果をもとにリスクグレード(G)を決定していくことになる．

4.5　Utility（有益性・実利）：U

その医薬品の妊娠女性における有益性・実利，いわばUtility の分類を Table 7 に示した．臨床現場の医薬品選択においては，通常は数多くある同効医薬品の中からの選択が行われており，上述したように，妊娠女性に対してはより安全で代替可能な医薬品の有無等が考慮される．そうした意味で，この Utility の視点は，適正使用においてきわめて重要なものと考えられる．

4.6　SEA 分類に Utility を加味した総合評価

SEA 分類に Utility を加味した総合評価を，FDA 分類等にならってＡ，Ｂ，Ｃ，Ｄ，Ｘの各カテゴリーに分類するための表を Table 8 に示した．従来のリスク分類にはなかった，臨床的対応の基準を示したものであり，高い有用性が期待される．

4.7　SEA 分類の記載方法

実際に医薬品の SEA 分類の結果を記載するときには，例えば「G2(S1・E0・A1)＋U0／総合評価：B」といった形式で，上述のすべての分類の記号を明示する形をとる．これにより，総合評価そのものはもちろん，その総合評価に至る過程での根拠情報がある程度すぐに理解することが可能になる．

5.　SEA 分類の医薬品添付文書の「使用上の注意」への記載について

上述してきたように，その医薬品の SEA 分類の結果を医薬品添付文書の「使用上の注意」に記載することにより，医師・薬剤師は当該医薬品の妊娠女性の使用に関する情報の概要（種類と内容・エビデンスとしてのレベル）とその評価（吟味の結果）を短時間で知ることができる．したがって，妊娠女性における医薬品の適正使用情報を臨床現場に届ける一つの手段として，きわめて有用と考えられる．

6.　おわりに

妊娠女性に対する医薬品の適正使用情報を臨床現場に届けること，それは妊娠女性とその児の利益に直結するものである．その一つの手段として，我々は，このSEA 分類の医薬品添付文書への展開を提唱している．もちろん，今すぐの本分類の展開は困難かもしれないが，妊娠女性に対する医薬品の適正使用情報としての医薬品添付文書のあり方の議論のスタートとなれば幸いである．

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