# Pregnancy and cancer

Prof.dr Vesna Kesić

Medical Faculty, University of Belgrade; Department of Obstetrics and Gynecology,
Clinical Center of Serbia, Belgrade, Serbia

Malignant diseases develop, as a rule, in the advanced age. However, due to the increasing number of women who decide to postpone pregnancy, the association between the malignant disease and pregnancy attracts more attention, nowadays. During the period of 1970 – 2000, the mean age of women who give birth for the first time was increased by 3.5 years (from 21.4 to 24.9). (1) Since then, the postponement of first birth has become an ongoing process. During the last decade, the age at first birth in Europe has increased in average 2 years and today, ranges between 25 and 29 years. (2)

The incidence of malignant diseases during pregnancy is difficult to calculate due to the lack of central registries for these conditions. The risk of association of pregnancy with a malignant disease is approximately 0.1% (1 case per 1, 000 deliveries). (3) It is hard, however, to determine total number of pregnancies in the population, and thus the incidence of malignant diseases during pregnancy is expressed per number of deliveries. According to a Swedish retrospective study on cancer during pregnancy the incidence rate is 37,4 cases per 100 000 deliveries. (4) Generally, the most frequent cancers are cervical cancer, melanoma, hematological malignancies and breast cancer, with incidence of all malignant diseases during pregnancy being approximately 21-38 cases/100 000 pregnancies.

Management of cancer during pregnancy is difficult. Both diagnostic and therapeutic interventions must be performed carefully, having in mind risk factors associated with both pregnant women and the fetus.

Pregnancy-associated malignant disease brings a range of the specific problems, such as:• Difficulties related to diagnosis and staging of the disease

• Risk of therapeutic interventions during pregnancy

• Supportive care of pregnant women with cancer

The factors influencing the treatment in pregnant women with malignant disease include:

 Gestational age - fetal viability

 Cancer stage and associated prognosis

 Possible adverse effects of treatment on the fetus, including potential, late occult problems

 Maternal risk associated with postponing of treatment in order to achieve fetal viability

 Fetal risk associated with premature delivery in order to enable timely cancer treatment.  Possible need of termination of pregnancy in early stage in order to enable optimal possibilities for treatment of malignancy

The treatment which is essential for women may be highly dangerous or even fatal for the fetus. Therapeutic options in malignant tumors during pregnancy are limited and none of them is ideal. Over the last years the concept of treatment of malignant diseases in pregnancy has evolved from complete negligence of pregnancy and frequently immediate termination of pregnancy to much serious approach aimed at reduction of risk of mortality or injury for both mother and the unborn child.

Four gold rules in treatment of malignant diseases in pregnancy are the following (5):

1. The attention must be paid to maternal well being

2. Curable malignant disease must be treated

3. Fetus must be protected from noxious effects of the treatment

4. It is necessary to attempt to preserve reproductive system of the woman.

Plan of the procure must be formulated within the medical, moral, ethical, legal and religious frameworks acceptable for the patient. Help to a woman to make appropriate choice necessitates absolute sincerity and most accurate information. The way in which the information is presented will influence the decision to be made by the patient. The procedure in malignant diseases during pregnancy necessitates not only scientific

knowledge on the risks associated with treatment based on the facts but also the art of communication with patients and above all high dose of humanity.

REFERENCES

1. Mathews TJ, Hamilton BE: Mean age of mother 1970-2000, Natl Vital Stat Rep, 2002; 50: 1-13

2. Frejka S, Sardon JP. First birth trends in developed countries: persisting parenthood postponement. Demographic Research, 2006; 15: 147-180

3. Pentheroudakis G, Orecchia R, Hoekstra HJ, Pavlidis N and on behalf of the ESMO Guidelines Working Group. Cancer, fertility and [pregnancy: ESMO Clincal Practice Guideliens for diagnosis, treatment and follow-up. Ann Oncol, 2010; 21 (suppl 5): v266- v273. doi: 10.1093/annonc/mgq198

4. Andersson TM, Johansson AL, Hsieh CC, Cnattingius S, Lambe M. Increasing incidence of pregnancy-associated breast cancer in Sweden. Obstet Gynecol , 2009; 114: 568- 5724.

5. Pavlidis NA: Coexistence of pregnancy and malignancy. The Oncologist, 2002; 7: 279- 87

6. Halaska M, Kesic V, Rob L. Pregnancy and Cancer. In ESGO Textbook of Gynaecological Oncology 3 rd edition, Ayahan A, Reed N, Glutekin M and Dursun P eds. Gunes Publishing, Ankara, Turkey. 2016;160

# Adenocarcinoma in situ (cervix)

## From diagnosis to treatment

J. Silva Couto

IPO- Coimbra, Portugal

Adenocarcinoma in situ (AIS) of the uterine cervix is caused by infection with highrisk human papillomavirus and is the recognized precursor of invasive adenocarcinoma of the cervix. Because most AIS lesions are caused by HPV 16/18/45 infection, prophylactic HPV vaccination is an important step toward prevention of AIS, potentially reducing the incidence of invasive adenocarcinoma. Nonetheless, at the moment the incidence of AIS and invasive adenocarcinoma continues to increase, especially among young women when fertility preservation is an issue. Both diagnosis and treatment of AIS is challenging, because AIS lesions frequently extend into the endocervical canal, making detection and complete excision difficult. Hysterectomy remains the standard treatment for AIS.

Selected patients, who wish to preserve fertility, with clear margins and negative ECC after initial conization are potential candidates for conservative treatment. If margins are involved after initial conization or ECC results are positive, the risk of residual or recurrent AIS and invasive adenocarcinoma of the cervix is considerably high. In these women, repeat surgery should be performed.

# TWIN–TWIN TRANSFUSION SYNDROME

Cihat Şen

TURKEY

Twin-to-twin transfusion syndrome and selective-IUGR are the most common clinical poblems. Monochrionic twins share same placenta and frequently have anastomotic vessels between two fetal circulations. Time to time a litte amount of blood exchange is possible but in a balance. In some cases about 10-15% of monochorinics are showing twin-to-twin transfusion syndrome. In TTTS situation, exchange of blood between two fetuses can become unbalanced and one fetus may supply of some blood to recepients (same cotiledon may be supplied by the donors and vein goes to other (recepient). Mostly TTTS cases are apperent clinically at 16-26 weeks of gestation. IUGR definition is below 10th centile according to the gestational age and there are more than 25% weight discordance in most cases but this should not be used as definition of selective IUGR. Incidence of selective-IUGR in monochorionics is about 7%. If there is a danger for fetal loss before viability mostly before 28th week, cord occlusion is the choice of procedure. It is not easy to explore those cases because Doopler findings is different than those of dichorionics and singleton and need special follow-up and interventions.
Twin–twin transfusion syndrome affects approximately 10% of monochorionic twins and accounts for the majority of morbidity and mortality in monochorionic gestations. Management options depend on gestational age, stage of disease, and availability of resources. Fetoscopic laser photocoagulation has been shown to be superior to amnioreduction in a randomized controlled trial and is considered the treatment of choice for severe twin–twin transfusion syndrome.
The procedure is usually offered between 16 weeks 0 day and 26 weeks 0 day of gestation. Some centers will offer laser therapy at stage I for symptomatic polyhydramnios, recipient cardiomyopathy based on specific echocardiographic scoring systems, or a shortened cervix. The procedure is typically performed with intravenous sedation and local anesthesia or under regional anesthesia. Patients are usually admitted for 24-hour postoperative observation. Maternal complications such as placental abruption (1%) and intraabdominal leakage of amniotic fluid (3%) are relatively low, and recovery is

generally swift. Preterm premature membrane rupture complicates approximately 30% of cases.

In severe disease, overall perinatal survival without treatment has been reported to be approximately 30%. As with most surgical procedures, a clear learning curve has been documented for laser photocoagulation. Emerging centers report dual survival rates of approximately 50%, whereas more experienced centers achieve a dual survival rate approaching 70%. The incidence of major neurologic abnormalities improves with surgical experience, achieving a rate as low as 6% in survivors, near the baseline for uncomplicated monochorionic gestations. This is likely the result of the fact that intertwin connections on the chorionic surface of the placenta are visually identified and ablated, thereby disrupting intertwin flow. Complete placental separation ("dichorionization") is unlikely, however, because anastomoses often occur below the chorionic plate and are therefore not visible at fetoscopy. Incomplete separation is evidenced by recurrent twin–twin transfusion syndrome (14%) and the development of twin anemia polycythemia sequence (13%). Recent technical improvements such as laser coagulation of the entire vascular equator, or "Solomonization," have led to incrementally improved outcomes with an overall survival rate of 75% and an incidence of recurrent twin–twin transfusion syndrome and twin anemia polycythemia sequence of 1% and 3%, respectively.

After treatment, weekly ultrasound surveillance with middle cerebral artery peak systolic velocity measurements to assess for recurrent twin–twin transfusion syndrome or the development of twin anemia–polycythemia sequence for 6 weeks is recommended and then ultrasound surveillance every 2 weeks as with uncomplicated monochorionic gestations.

Most treatment centers recommend delivery of treated twins at 36 weeks of gestation, whereas singleton survivors may progress to 39 weeks of gestation. Patients should be made aware that the risk of an adverse outcome such as single or dual demise, treatment failure, or long term survivor morbidity is significant. Laser coagulation offers the highest likelihood of intact twin survival for severe disease.

Serial amnioreduction is associated with an approximate 60% survival rate and a 25% risk of neurologic morbidity among survivors. The intent of amnioreduction is to decrease intraamniotic pressure, thereby decreasing the risk of preterm labor or preterm premature membrane rupture, improving uteroplacental perfusion, and decreasing maternal symptoms. The major disadvantage of amnioreduction, however, is that it does not address the underlying pathophysiology of anasthomosis.

Selective feticide is most commonly performed when the twins are discordant for a major structural

abnormality or one of the twins is under very severe IUGR and heart failure. The death of one of a pair of monochorionic twins can result in neurologic damage to the surviving co-twin. In high-stage disease, selective feticide may provide the highest likelihood of intact survival by allowing pregnancyprolongation. Other indications for selective feticide include severe selective fetal growth restriction or to prophylactically avoid the potential complications of monochorionic gestation. Methods include bipolar cord coagulation, laser cord photocoagulation, intrafetal laser photocoagulation, or intrafetal radiofrequency after 16 weeks of gestation. Intrafetal laser ablation is technically easier to perform than bipolar cord coagulation and is associated with a lower rate of procedure-related complications.

There is also insufficient evidence to inform decision-making regarding timing of delivery, but most centers recommend allowing the pregnancy to proceed to term. Routine monitoring for maternal coagulopathy is not indicated.

Expectant management: This may be appropriate for early disease (stage I), or late in gestation, and when frequent ultrasound surveillance is available. The optimum management of stage I disease has not been determined. A small retrospective study demonstrated improved neurologic function, but not overall survival, with fetoscopic laser photocoagulation for stage I disease. Expectant management may be the only available option when operative intervention before viability is unavailable.

The peak incidence of twin–twin transfusion syndrome is 19 weeks 6 days of gestation, but can occur any time thereafter. Delivery is a good option in the mid- to late third trimester. Iatrogenic delivery may be the only available option when other alternatives for safe pregnancy prolongation in late pregnancy are unavailable and there is concern for imminent demise of one twin or maternal health declines.

TRAP-Twin Anemia Polycythemia Sequence

Chronic slow and unbalanced blood transfusion between monochorionic fetuses results in twin anemia polycythemia sequence. It is characterized by anemia of the “donor” twin and polycythemia of the “recipient” twin without amniotic fluid discordance. Prenatal diagnosis of fetal anemia and polycythemia is possible by middle cerebral artery peak systolic velocity measurements by Doppler. Diagnosis of twin anemia polycythemia sequence is made when middle cerebral artery peak systolic velocity of one twin is greater than 1.5 MoM and the peak systolic velocity of the second twin is less than 1.0 MoM without polyhydramnios and oligohydramnios. It complicates approximately 3–5% of spontaneous

monochorionic twin gestations, but, up to 10-15%, after fetoscopic laser for twin–twin transfusion syndrome. It is believed to develop as a result of very small caliber, less than 1 mm in diameter, unidirectional arteriovenous connections, which are located close to the placental edges along with a paucity of arterioarterial vascular connections. Spontaneous twin anemia polycythemia sequence can occur any time during pregnancy but is frequently diagnosed after 26 weeks of gestation.
Depending on gestational age, certain management alternatives can be considered including expectant management, selective feticide, delivery, intrauterine transfusion with or without partial exchange transfusion for the polycythemic fetus, and fetoscopic laser photocoagulation. The utility of intrauterine transfusion was investigated in the past for symptomatic relief of the anemic fetus., but the underlying vascular connections continue to exist and the polycythemia may worsen in the recipient twin. Furthermore, there are reports of skin necrosis in cases treated with multiple intrauterine transfusions. The median time from diagnosis to delivery was significantly prolonged in the laser group. In appropriately selected cases, either fetoscopic laser may be the best treatment options at present, but management must be individualized based on findings and gestational age.