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Fetal therapy – Multiple choice answers Vol. 58

1. a) F b) T c) T d T e) F

The performance of prenatal ultrasonography in identifying congenital obstructive uropathy remains unsatisfactory. The sensitivity was only around 51% and around one quarter of prenatal suspicions of LUTO was normal at birth or reclassified as other non-obstructive uropathies, with renal reflux being the common final diagnosis, after postnatal examination. The chance of spontaneous resolution before 20 gestational weeks is 90% in longitudinal bladder length of 7–15 mm (with normal karyotype) at 10–14 gestational weeks. In a systematic review including 13 studies and 215 women with confirmed LUTO postnatally, the best predictive parameters at diagnosis for postnatal renal function were renal cortical appearance and the presence of oligohydramnios.

The first urine sample obtained by vesicocentesis represents urinary stasis for prolonged periods of time.

2. a) T b) T c) T d T e) T

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3. a) F b) F c) T d) F e) T

The major advantages of fetal cystoscopy over vesico-amniotic shunt are direct visualization of the bladder neck providing diagnostic identification of the underlying pathology and specific therapeutic treatment can be offered at the same time. The information obtained aids prognostic counselling to the women. In addition, relieving the obstruction during fetal life can allow a more 'physiological' drainage of urine. During the procedure, transurethral stenting of urethral stenosis or ablation of the posterior urethra value can be performed. Fetal intervention can improve perinatal survival but survivors may have a high rate of renal impairment. A true curved sheath allows adequate access to the fetal bladder neck and subsequent correct angle to apply laser to the posterior urethral valve.

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4. a) F b) F c) T d) T e) T

Higher lesions, hindbrain herniation and bilateral ventriculomegaly are all indications for surgical intervention. Subsequent pregnancy management after open fMMC closure includes sonographic monitoring of the hysterotomy site, repeat cesarean delivery at 37 weeks and a minimum 2 year inter-delivery interval.

5. a) T b) T c) T d) F e) F

Open fetal MMC closure is associated with a decreased subsequent need for shunting, reversal of hindbrain herniation and improved neurologic function. Premature delivery rates are higher than normal though there is no evidence of increased rates of chorioamnionitis.

6. a) F b) T c) T d) T e) T

The small body size of the human fetus ensures a relatively high cell dose. The fetal circulation ensures that stem cells are not entrapped in the lungs which is a major issue in postnatal transplantations. Due to the normal migration of stem cells during fetal life it is assumed that these compartments could be available for homing of external stem cells. There is evidence that before the second trimester the human feus has a rather naïve immunological function that may inhibit rejection of a foreign graft. The intrauterine environment is relatively sterile and protective for the fetus.

7. a) T b) T c) T d) T e) F

All punctures of the uterus and products of conception carry a risk of perforation of maternal organs. Most common is accidental puncture of small bowel that may lead to contamination of the fetus. All punctures of the fetal body carry a risk for fetal bleeding. Although rare, it can be potentially fatal. Puncture through the mother and transplacental passage of cells from fetus to the mother might expose the mother to allogenic donor cells and the risk of immunization. The fetus can be immunized when exposed for foreign HLA antigens. A sibling will not face any risk of being immunized.

8. a) T b) T c) T d) T e) F

To use the fetuses own stem cells will ensure no immunological reaction. Stem cells from, for example amniotic fluid, could easily be retrieved and manipulated. Possibly ex-vivo gene therapy carries a lower risk for germ cell transduction which is a reality for in-vivo gene therapy. Possibly ex vivo manipulation also carries a reduced risk of maternal contamination which potentially could cause transduction of maternal cells. There is no evidence that fetal stem cells are more prone to be manipulated with gene therapy than adult stem cells.

9. a) T b) F c) T d) T e) F

A complete prenatal workup including advanced imaging and advanced genetic testing (micro arrays) is recommended before any personalized prenatal prediction of outcome. In about 10% of cases an associated anomaly that was missed at first scan was detected at a centre with a high load of CDH cases. Genetic testing is mandatory for accurate counselling, future pregnancies and eligibility for prenatal therapy. A genetic aetiology can be identified in up to 35% of CDH cases by conventional karyotyping. However, an additional 9% of cases with normal karyotype have copy number of variants (CNVs) including small deletions and duplications identifiable by array comparative genomic hybridization

(array CGH) that are clinically relevant in some CDH cases. There are also syndromes that have no genetic signature yet. In centres offering FETO, personalized prediction is made based on the isolated nature of the defect, its side, estimation of the lung size, presence of liver herniation, and more recently stomach position may be included as well. In a study including 71 CDH cases, the differences in paired measurements of the lung areas by the same and two different observers were smaller when the manual tracing method was used than with the approach of multiplying diameters. A more recent study confirmed these results. Almost all cases of RCDH have liver herniation, therefore it cannot be used as a predictive parameter.

10. a) F b) T c) F d) T e) F

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11. a) F b) T c) F d) T e) T

FETO currently is considered as an experimental therapy for CDH by most centres. It is being assessed in two randomized clinical trials (RCT) "Tracheal Occlusion To Accelerate Lung growth" (www.TOTALtrial.eu), in fetuses with LCDH and severe or moderate lung hypoplasia (NCT01240057 and NCT00763737). Prenatal balloon removal is associated with greater survival and lesser morbidity. In addition, it avoids unplanned, emergency balloon retrieval procedures and it permits the patient to return to the referring tertiary centre for delivery. In a series on 311 balloon removals, the only deaths occurred (three) when balloon removal was attempted outside the FETO centre. In a series on 211 FETO cases, preterm premature rupture of membranes occurred in 47%. Fetal tracheomegaly is common but does not seem to have a clinical impact besides a barking cough that decreases with time. Reported adverse events and side effects from FETO series are rare, with the exception of very early occlusions and complications during emergency balloon removal. FETO was initially performed under epidural anesthesia. Today, the procedure is typically performed under local anesthesia with conscious sedation optional, yet loco-regional can be done when clinically required.

12. a) T b) T c) T d) T e) T

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13. a) T) F c) T d) T e) T

Airways compromise is the most severe and life threatening complication in cases of neck tumour. Ensuring airway patency in cases of neck tumour is paramount. EXIT carries significant risk for the mother, such as excessive blood loss, uterine atony and infection. Indeed, these risks led to the development of fetoscopic laryngo-tracheoscopy. This less invasive procedure allows an optimal

evaluation of the fetal airways. It can be complemented with fetoscopic intubation and therefore in some cases avoid an EXIT procedure. Once airways patency is secured, the need for postnatal surgery is to be evaluated. In cases of large tumours, postnatal surgery is generally warranted.

14. a) F b) F c) T d) F e) T

Both CCAM and BPS lesions typically grow until 26–28 weeks and then spontaneously regress. However, they can grow fast and cause fetal distress. In those cases, prenatal intervention is warranted given the high mortality rate (approaching 95% in case of hydrops). Steroids alone are used for microcystic CCAM. Intrafetal laser coagulation, coiling and radiofrequency ablation are less invasive, and have mostly replaced open fetal surgery.

15. a) T b) T c) F d) T e) T

Sacrococcygeal teratoma (SCT) is the most common congenital tumour with a prevalence of 1 in 27000 live births. It is more frequent in females. Whereas SCT are frequently detected before birth, metastases are not. This is a challenge in the prenatal management and in-utero therapy. A solid tumour volume to head volume ratio >0.12, tumour volume to fetal weight ratio >0.12 prior to 24 weeks, together with rapid tumour growth have been identified as predictors of cardiac failure and hydrops. High cardiac output is a condition that, untreated, leads to hydrops and eventually in utero fetal death. Fetal tumours, in particular highly vascular solid SCT, can have a high vascular demand and therefore lead to fetal hydrops.

16. a) F b) T c) T d) T e) T

Despite opening the aortic valve and improving forward flow through the left heart, there is no evidence of left ventricular growth. The selection criteria now advise that a fetal left ventricle should be no smaller than a Z score of −2, so it will be capable of supporting the systemic circulation after birth. The definition of a technically successful procedure is to demonstrate forward flow through the aortic valve and often new regurgitation on color Doppler. Opening the aortic valve will improve opening of the mitral valve (provided it is not too damaged) and reduce the pressure required to fill the left ventricle, the left ventricular loading pressure. The improved forward flow through the left heart will result in more forward flow through the mitral valve and an increase in its filling time. The improvement in right and left heart haemodynamics reduces systemic venous pressure and leads to improvement, or total resolution of fetal hydrops, thus potentially increasing the duration of pregnancy.

17. a) F b) F c) T d) F e) T

Mid-trimester screening of the fetal heart may detect as few as 10% of babies born with aortic valve stenosis. The signs may be subtle at screening, but often include left atrial and ventricular dilation (sometimes misinterpreted as hypoplastic right heart disease). While the aortic valve may be bicuspid in cases of aortic stenosis presenting in childhood, fetal aortic stenosis is characterized more commonly by its effects on the left ventricle and mitral valve. These include dilation of the left ventricle and endocardial fibroelastosis and ischaemic damage to the mitral valve resulting in mitral dilation and left atrial enlargement. Successful fetal valvuloplasty results in improved forward flow through the left heart and maintenance of growth of the aortic valve. However, almost all neonates will require either repeat aortic valvuloplasty or commonly between one and three surgical procedures on the aortic valve and left ventricle to maintain a biventricular circulation. An unknown proportion of fetuses with early

to mid-second trimester aortic stenosis progress to HLHS. This progression is defined by closure of the mitral and aortic valves and involution of the supporting left ventricle and progressive narrowing of the ascending aorta and transverse aortic arch. Thus at term these neonates have extensive left heart disease only suitable for a univentricular circulation.

18. a) F b) T c) T d) T e) T

A prenatal diagnosis of aortic stenosis or HLHS does not usually confer a survival advantage because prenatal diagnosis may be commoner in more severely affected hearts as well as in fetuses with multiple anomalies. Additionally termination of pregnancy or no postnatal treatment may be chosen by parents. More recent reports using propensity scoring suggest circulatory outcomes following a technically successful fetal valvuloplasty for aortic stenosis are similar to the natural history of the fetal disease. These assess the advantage in live births, excluding the procedure related mortality of about 10% in experienced centres and up to 30% in others. Pulmonary hypertension may result from damage to the pulmonary veins, due to a restrictive atrial septum or endocardial fibroelastosis leading to increased left ventricular loading pressure. The resultant pulmonary damage has a severe impact on postnatal treatment: surgery is associated with high mortality, or may not be offered. Postnatal aortic valvuloplasty is now performed with a low risk (below 5% mortality) in good candidates. As the selection of cases suitable for fetal valvuloplasty moves towards only choosing those with good left ventricles, it is plausible that fetuses will be offered valvuloplasty that would fare as well without.

19. a) T b) F c) T d) T e) F

Unilateral pleural effusion with significant mediastinal shift is indicative of a significant mass effect and should be decompressed urgently. Fetal hydrops with predominant fluid accumulation in the pleural spaces and upper body oedema, is suggestive of pleural effusions as the primary underlying etiology of hydrops, which may potentially be reversed with shunting and thus should be attempted. Rapidly enlarging effusions with new polyhydramnios is also suggestive of significant mass effect with oesophageal compression causing impaired swallowing and polyhydramnios, which increases the risk of preterm rupture of membranes and birth; therefore fetal intervention should be strongly considered.

20. a) T b) F c) F d) T e) T

Currently ultrasound and magnetic resonance imaging cannot reliably predict pulmonary hypoplasia antenatally, which remains the main source of postnatal morbidity and mortality in affected fetuses. Sonographic prognostic indicators used in other conditions for prediction of pulmonary hypoplasia have not been validated in fetuses with pleural effusion, such as lung-to-head ratio in congenital diaphragmatic hernia and thoracic circumference in lethal skeletal dysplasias.

21. a) T b) F c) F d) F e) F

Peripartum thoracocentesis may be considered with large and rapidly expanding effusions, as some case series have demonstrated this to be beneficial for postnatal resuscitation. Mode of delivery does not impact neonatal outcomes, and therefore a vaginal delivery is encouraged with reservation of Caesarean section for standard obstetric indications. Delivery must occur in a tertiary care centre with adequate neonatal and paediatric support capable of resuscitating an infant, specifically with the ability to insert a chest tube urgently and provide mechanical ventilatory support if needed. A detailed postnatal examination is also indicated to evaluate for additional abnormalities and genetic syndromes. Shunts should be clamped immediately at birth to prevent a spontaneous pneumothorax.

22. a) F b) F c) F d) T e) F

Technical aspects for obtaining MCA-PSV are defined by the International Society of Ultrasound in Obstetrics and Gynecology (ISUOG) guidelines. An axial section of the brain, including thalami, cavum septi pellucidi and greater wing of sphenoid, with the circle of Willis identified by color Doppler, should be obtained. The MCA is sampled at or near its origin from the internal carotid artery. The waveform peak is measured, with the angle of insonation as close as possible to 0°.

23. a) F b) T c) F d) T e) F

In a recent institutional series of 1678 intrauterine transfusions perinatal survival rose from 88.6% in 1988–2000 to 97.0% in 2001–2015; in the same time intervals, the procedure-related fetal loss rate declined from 4.7% to 1.8% per fetus and from 1.6% to 0.6% per procedure. Arterial puncture, needling of a free loop of cord, and not using fetal paralysis were identified as a risk factors for complications.

24. a) F b) F c) F d) F e) T

Recently, Zwiers et al. reviewed the complication rates of intrauterine transfusions in cohort studies published in the last ten years: the observed a complication rate of 7.8% per fetus and 2.7% per procedure; the procedure-related fetal loss rate was 2.1% per fetus and 0.7% per procedure; overall, the live birth rate was 95.5%.

25. a) F b) F c) T d) F e) F

The Solomon technique can be used for anterior and posterior placentas. Successful laser coagulation in TTTS depends on appropriate visualization of the vascular equator, regardless of the technique. The Solomon trial showed a significant reduction of TAPS and recurrent TTTS without differences in survival rates. The trial was underpowered to find a significant difference in perinatal mortality. This represents exactly the description of the Solomon technique. The rationale of this method is coagulation of the whole vascular equator (including tiny anastomoses that might not be visualized). Some authors made the critical comment that the surgeons should prevent unnecessary sacrifice of placental tissue during laser treatment. Recently the “Solomon” technique was found to be associated with a higher risk of placental abruption.

26. a) T b) T c) T d) F e) T

Whereas inter-twin anastomoses are found in all MC placentas, TTTS occurs only in 10%–15% of MC pregnancies. The risk for the development of TTTS depends on the type, number and diameter of the anastomoses. TTTS is definitely a severe complication and if left untreated, perinatal mortality is 80–90%. In a RCT, Senat and coworkers compared serial amnioreduction vs fetoscopic laser surgery and found significantly higher survival, increased gestational age at delivery and improved neurodevelopment after laser treatment. Therefore, laser surgery has become the first-line therapy. High volume fetal medicine centres have shown improved outcome in the last 25 years in terms of double survival rates after laser surgery. There is growing evidence that centralisation with at least 20–30 procedures per surgeon annually is needed to maintain high quality. Stage I cases do not necessarily progress to more advanced stages, but bladder filling of the donor is not per se a sign of good prognosis. There is no evidence that amnio-reduction is better than laser treatment or expectant management in these cases. High focused ultrasound may be a non-invasive treatment for TTTS in the future. In an animal model placental vessels have been closed using this technique.

27. a) T b) T c) F d) T e) T

Polyhydramnios of the recipient twin leads to a rapid increase in uterine size and abdominal tension. In most cases TTTS occurs between 16 and 26 weeks of gestation. Therefore, ultrasound should be performed at least every second week and amniotic fluid assessment is indicated in both sacs. Mono-amniotic twins are rare and TTTS develops less frequently than in di-amniotic MC twins, owing to a system of abundant anastomoses, which is less prone to cause imbalances. Prematurity seems to be the major risk factor for neurodevelopmental impairment in survivors after laser treatment.

28. a) F b) F c) F d) T e) F

A large prospective screening study in Norway has shown that of all occurring HPA-1a allo-immunisations in HPA-1a negative pregnant women, 75% occur during or after delivery. Screening women 6 weeks post-delivery could identify these women, and preventive measures could be taken in the subsequent pregnancy. Such program however would miss all cases (around 25%) of FNAIT occurring during the first pregnancy. In the past, fetal ICH due to FNAIT was thought to occur predominantly between 30 and 35 weeks' gestation. However, recent data show that ICH often occurs before 28 weeks. Thus, to enable preventive measures, first trimester screening is better than screening at 27 weeks. Pre-pregnancy screening may identify couples who are incompatible for HPA-type. At-risk women could then be followed up during pregnancy. We do know however that still, many pregnancies occur unplanned, therefore, such a program will fail to identify many women at risk for FNAIT.

29. a) T b) T c) F d) T e) F

The complex of aVB3 is present on early embryonic and placental tissue. Interaction of maternal alloantibodies against HPA-1a with syncytio-trophoblast cells early in pregnancy might lead to an impaired placental invasion and early loss of pregnancy. Increased rates of spontaneous miscarriage in FNAIT have been reported in several retrospective cohort studies. Also, studies with murine FNAIT models have shown an increased pregnancy loss. Intrauterine growth restriction, leading to a low birth weight, is a multifactorial condition that is associated with high morbidity. Frequently, its cause is unknown. Whereas HPA-1a is present on syncytio-trophoblast cells, it is in direct contact with the maternal circulation, containing the *anti*-HPA-1a alloantibodies. Therefore, it is likely that an interaction between the antibodies and fetal HPA-1a on placental tissue might impair placental function. This impairment of placental function might lead to several conditions, including intrauterine growth restriction. Several cohort studies, retrospective as well as prospective, have reported such a correlation and mouse models confirmed a possible association as well. Intrauterine infections are known to lead to a neonatal thrombocytopenia, which is an important hallmark of FNAIT. However, interaction of maternal *anti*-HPA-1a alloantibodies is not correlated with causing an infection in itself. Angiogenesis is important for the developing fetus, especially the fetal brain. The aVB3 complex is not only present on placental tissue, but on endothelial cells as well. The interaction between maternal *anti*-HPA-1a and fetal endothelial cells might lead to an impaired endothelial function, which might lead to leakage as well as impaired angiogenesis. HPA-allo-immunisation is not associated with fetal bone development, hence HPA-1a is not known to be present on osteoblasts or other cells forming bone.

30. a) F b) T c) T d) F e) T

The most commonly used dose IVIG is still the same as the one proposed by Jim Bussel in 1988, which was 1 g per kg maternal weight per week. Proper dose-finding studies have not been performed. In women with a severe history, some clinicians choose to double this dose, which appears to have some

effect on fetal/neonatal platelet count in some studies, although a better protection against ICH is not proven. Results from a prematurely stopped RCT and a prospective registry suggest that a lower dose of 0.5 g per kg does not lead to worse outcomes, both in terms of average platelet count as well as on incidence of ICH. In all protocols, the dose is adjusted to maternal weight.