CORDOCENTESIS

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Cordocentesis or percutaneous umbilical cord blood collection is an invasive ultrasound-guided technique used for both diagnosis and fetal therapy that can be performed from 18-20 weeks of gestation. It consists of inserting a needle directly into the fetal circulation, specifically into the umbilical vein, under ultrasound guidance to obtain fetal blood (for hematological, genetic or biochemical study) or to inject medication or blood components directly into the fetal circulation. In experienced hands, the procedure is successful in >98% with a risk of fetal loss of up to 1%.

In this protocol we will differentiate diagnostic cordocentesis from therapeutic cordocentesis.

1. DIAGNOSTIC CORDOCENTESIS

1.1. Indications

The indications for cordocentesis have declined over recent years with the emergence of new molecular diagnostic laboratory techniques for genetic studies and Polymerase Chain Reaction (PCR) for viral infections. These techniques can be applied on amniotic fluid or chorionic villi, thus with more common techniques such as amniocentesis or chorionic villus sampling, and with results of equal or greater reliability.

1.1.1. Suspected fetal anemia

Suspected fetal anemia is the main indication for cordocentesis in our setting since it provides the only direct way to calculate fetal hemoglobin. Currently the suspicion of fetal anemia is made by the observation of a peak systolic velocity (PSV) of the middle cerebral artery (MCA) higher than 1.5 MoMs with or without fetal hydrops. If fetal anemia is suspected, a diagnostic cordocentesis will be performed with the possibility of intrauterine transfusion at the same time.

The main causes of fetal anemia are:

- Maternal isoimmunization: presence of maternal anti-fetal erythrocyte membrane antigen antibodies (anti-D, anti-Kell, anti-c). Since the routine use of anti-D gammaglobulin in Rh-negative pregnant women, the incidence of anti-D isoimmunization has decreased dramatically. For this indication we will not perform cordocentesis or intrauterine transfusion beyond 35.6 weeks detailed in chapter 'Isoinmunization')
- Parvovirus B19 infection
- Other rare causes of fetal anemia requiring intrauterine transfusion
- Congenital anemias of monogenic origin, including alpha-thalassemia, which in Southeast Asia is a frequent cause of fetal hydrops.

1.1.2. Biochemical diagnoses

On rare occasions, cordocentesis may be performed for the following indications:

- Thyroid function study: in fetuses with suspected hyperthyroidism (maternal hyperthyroidism and evidence of fetal goiter), in order to indicate intrauterine treatment as appropriate.
- Study of renal function: Cystatin C and beta-2-microglobulin in fetal blood can potentially be evaluated in fetuses with ultrasound diagnosis of renal dysplasia to assess renal function more sensitively than in amniotic fluid.

1.1.3. Fetal thrombocytopenia

Alloimmune thrombocytopenia is the destruction of fetal platelets by the transplacental passage of maternal antiplatelet antibodies, usually anti-HPA-1a, caused by feto-maternal incompatibility. The main complication of alloimmune thrombocytopenia is intracranial hemorrhage (10-30%), fetal death in 10% of cases and irreversible neurological sequelae in most cases. The diagnosis of fetal alloimmune thrombocytopenia can only be made by cordocentesis to assess fetal platelet count. Phenotyping of platelet antigens can be established by amniocentesis or fetal DNA in maternal blood. The use of cordocentesis in this condition is now limited to diagnosis. Platelet administration, formerly used in this condition, has been abandoned in favor of treatment (or prophylaxys in a new pregnancy if there is history of a previously affected one) with intravenous maternal immunoglobulin 1g/kg/week in combination or not with corticosteroids to increase the fetal platelet count. The use of cordocentesis prior to delivery in pregnancies where a prophylactic treatment has been given is normally not recommended as routine practice, because immunoglobulin therapy has been shown to work in a extremely high proportion of cases.

1.1.4. Non-immune hydrops fetalis

The differential diagnosis of fetal hydrops includes a large list of causes, being anemia, aneuploidy and infection among the most common. Currently, ultrasound, amniocentesis and maternal laboratory tests are the first diagnostic step. Cordocentesis with possible intrauterine transfusion is reserved to cases with suspicion of anemia (i.e. with a PVS ACM >1.5 MoMs).

1.1.5. Fetal infection

- Rubella: Currently the only indication for cordocentesis for the diagnosis of fetal infection is suspicion of rubella (positive maternal serology and negative PCR in amniotic fluid). Low viral load in amniotic fluid is frequent, and in these cases cordocentesis for IgM in fetal blood will be performed after 22 weeks (before 22 weeks the fetus rarely produces IgM).
- Cytomegalovirus: classically cytomegalovirus (CMV) infection was an indication for cordocentesis for platelet count and liver profile study (GGT) in fetal blood as it correlated with fetal prognosis. Currently, neurosonography and magnetic resonance imaging are better prognostic indicators. Cordocentesis for CMV infection should be performed on an individual basis, evaluating the risk-benefit with the parents (detailed in chapter 'TORCH infections')

1.1.6. Genetic analysis

As mentioned, the use of cordocentesis is now limited to fetuses with an indication for genetic study in the presence of oligo/anhydramnios, where amniocentesis or chorionic villus sampling are challenging or unfeasible.

1.2. Procedure

Diagnostic cordocentesis is normally performed as an outpatient procedure. In very selected cases, it can be performed in a setting where a cesarean section can be performed (i.e. severely hydropic fetuses at viable gestational ages). The following steps must be followed:

- Check that a detailed explanation of the procedure and potential complications has been offered to parents and informed consent is complete.
- Check of maternal Rh type and HIV, HBV and HCV infection serological status. Invasive procedures must be carefully considered and can be contraindicated in the event of maternal HIV, HBV and HCV infection (see specific protocols for considerations on viral load and discussion about risks and benefits with parents).
- Consider fetal lung maturation with corticosteroids if gestational age between 26 and 34 weeks in the absence of severe anomalies.
- Detailed ultrasound, with complete fetal anatomical study (if not previously done), and localization of the placental insertion of the umbilical cord.
- Skin preparation of the maternal abdomen with Chlorhexidine. Scrubbing of operators. Ultrasound probe cover sheath and sterile gel are used.
- Maternal sedation or prophylactic antibiotics are not routinely used.
- Maternal anesthesia is not routinely indicated. If used, 5 ml of levobupivacaine 2.5mg/ml + 5 ml of saline.
- Intramuscular fetal anesthesia is not routinely used. It can be given if the puncture is potentially complex or intrahepatic puncture (>24 weeks of gestation): Fentanyl 10-15mcg/Kg + Rocuronium 0.6-1.2mg/Kg + Atropine 20mcg/Kg .
- Needle: 20 Gauge. The ideal choice is a 15 to 20 cm needle for fetal procedures (if possible with echo-tip). A standard spinal needle (normally about 10 cm long) can be used in transplacental procedures, where the cord insertion can be very close to the skin. Needles of smaller diameter (i.e. 22 Ga) are not recommended due to the difficulty of maneuvering the needle once it has been inserted in the uterus.
- The procedure is done following a "free-hand" technique, which allows to reposition the direction of the needle at any time. The target vessel (vein if cord insertion or intrahepatic vein) must be thoroughly examined with 2D ultrasound and color Doppler, and the trajectory of the needle to reach the targe carefully calculated in advance several times before puncturing the skin, in order to avoid as much as possible manipulation or excessive maneuvering while the neddle is in the uterus.
- For cases with anterior placenta, the puncture is done transplacentally at the placental insertion of the cord, puncturing the vein.
- For posterior or lateral placentas, puncturing the intrahepatic vein is the preferred choice if the fetal position allows for it. The second choice is puncturing the cord, which must be done as close as possible to the placental insertion or (if there is no other choice) the abdominal insertion, but even clean and quick punctures may result in intraamniotic bleeding. A maximum of 3 attempts are performed for a period of 20 minutes.
- Once the needle is positioned, 3-5ml of fetal blood are drawn depending of gestational age and tubes required for the specific analyses of each case. Remember that feto-placental volume is very small so that the smallest amount of blood must be drawn.

1.3. Complications

In experienced hands, cordocentesis has a high rate of mild/temporary complications and a small (1% or less) rate of severe complications.

- **Hemorrhage at the puncture site:** this the most frequent complication (20-50%) when a cord loop is punctured in the amniotic sac. Unless there is a severe tearing of the cord, hemorrhage is self-limiting in all cases within minutes, but it can lead to fetal anemia. Hemorrhage is a virtually non-existing problem in transplacental umbilical vein (unless the needle is accidentally advanced into the amniotic sac) or fetal intrahepatic vein punctures.
- **Bradycardia:** occurs in 5-10% of procedures and if it is not the consequence of a severe hemorrhage is normally a transient phenomenon. The mechanism can be a vasospasm of an umbilical artery or a vagal fetal reaction in case of fetal puncture. Bradycardia may be more common in very preterm fetuses. If bradycardia is severe and persisting in a viable fetus, emergency cesarean section may be considered. Obviously, this possibility must be foreseen before the procedure and discussed appropriately with parents.
- **Intrauterine fetal death**: it is a very rare complication (1%), and it is normally preceded by severe bradycardia. There is a higher risk (up to 5-15%) in very preterm or pre-viable fetuses, those complicated with hydrops or those with obvious malformations.
- **HIV, HBV or HCV vertical transmission**: as mentioned above, cordocentesis is not indicated in HIV, HBV or HCV seropositive mothers. Cases where there is no alternative to cordocentesis (maternal isoimmunization with fetal anemia) can be discussed with parents and be ideally performed in with an undetectable viral load. In those cases, transplacental puncture should be avoided.
- **Other less frequent complications**: chorioamnionitis, placental abruption and umbilical cord hematoma have been described, but are very rare.

1.4. Follow-up

- Cardiotocographic monitoring at the end of the procedure from 26 weeks on.
- Anti-D gammaglobulin if maternal Rh negative.
- Relative rest for 24h.
- Ultrasound assessment 24 hours after the procedure.

2. THERAPEUTIC CORDOCENTESIS

2.1 Intrauterine transfusion

Intrauterine transfusion is indicated when the fetal hematocrit is below 30%.

The amount of blood to be transfused is calculated during the procedure from the expected fetal blood volume according to the gestational age multiplied by a factor determined by fetal hematocrit and donor's hematocrit (http://fetalmedicinebarcelona.org/calc/).

The procedure is performed in an operating room.

2.2. Procedure

- Check that a detailed explanation of the procedure and potential complications has been offered to parents and informed consent is complete.
- Request blood for transfusion the day before the procedure from the blood bank together with maternal blood collection for compatibility testing. 0-negative blood, compatible with any antibody present in the mother's serum, from a CMV seronegative donor, de-leukocytized by filtration, irradiated and concentrated to a hematocrit between 75-85%.
- Fetal lung maturation if gestation >24 weeks (betamethasone 12mg/24h 2 doses).
- Previous ultrasound with evaluation of placental insertion and fetal position. Evaluate potential targets for puncture (see description of Cordocentesis) and cervical length.
- Nifedipine 20 mg (2 tablets) orally if cervical length< 15 mm.
- Maternal antibiotic prophylaxis with Cefazolin 2g.
- Maternal sedation under the care of anesthesiologist can be used. Otherwise, maternal pre-operative sedation with benzodiazepine can be considered.
- Field preparation with Chlorhexidine. The operators scrub and dress like for a surgical procedure (surgical attire, head cover and mask, sterile gloves). Ultrasound probe sheath and sterile gel are used.
- Preparation of the blood infusion line (Figure 1). The outflow line of the red blood concentrate is connected sequentially to: infusion line / 3-way stopcock / extension line (50-80 cm) / 3-way stopcock /extension line (10-30 cm). The last extension line will be connected to the needle during the transfusion. The first stopcock is connected to a 10 ml syringe used to aspirate blood from the blood bag and infuse it to the fetus. The second stopcock is used for blood testing during the procedure.

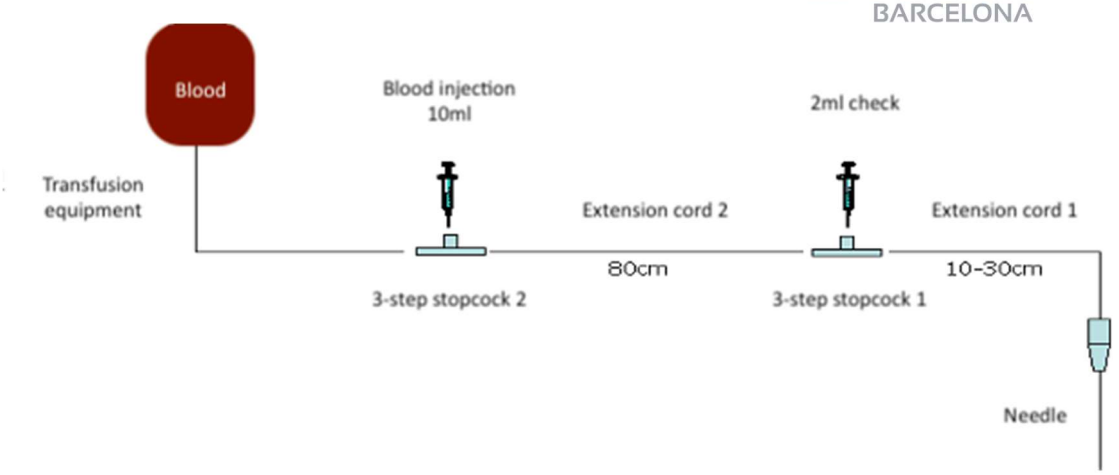

Figure 1. Intrauterine transfusion circuit set-up.

- Maternal local anesthesia is not routinely indicated.
- Fetal anesthesia: If puncture is transplacental, anesthesia can be given at the time of umbilical vein puncture (rocuronium 0.6-1.2mg/kg). If the puncture is in the fetal hepatic vein: Intramuscular fetal anesthesia with Fentanyl 10-15mcg/kg + Rocuronium 0.6-1.2mg/kg + Atropine 20mcg/kg.
- Ultrasound-guided percutaneous puncture with a 20G needle (see section 1.2. considerations about the needles in the description of diagnostic cordocentesis).
- The transfusion can be done in the umbilical cord vein through transplacental insertion (anterior and some cases of lateral placenta) or in the fetal intrahepatic vein (posterior or most cases of lateral placenta). Same comments as in section 1.2. of diagnostic cordocentesis apply.
- Once the fetal vessel is punctured, a first fetal sample of 1-2 ml (EDTA tube) is drawn from the second stopcock to check fetal hematocrit. While waiting for the result, in transplacental punctures, fetal anesthesia is given. , making sure that it is not diluted in amniotic fluid.
- Once the fetal hematocrit is received, calculation of the volume of blood to transfuse http://fetalmedicinebarcelona.org/calc/. If hematocryt is extremely low, consider amniotic fluid contamination (in transplacental insertion only). Normally, desired hematocrit value is set at 45%.
- Start blood transfusion under continuous ultrasound monitoring, The entire path of the needle, and specially the correct location of the tip of the needle inside the vessel, must be visualized by ultrasound plane during the whole procedure. The entry of blood into the fetal bloodstream is visualized as white bubbles on ultrasound. During periods when no blood is infused, fetal heart rate must be monitored if it is not visible in the ultrasound infusion plane.
- When approximately 75-80% of the blood calculated has been infused, check if fetal hematocrit has increased as expected: (1) draw 2 ml from the second stopcock to purge the circuit (which is full with high hematocrit blood) and reserve them, (2) draw a second 2 ml sample, which is use them for analysis, (3) replace the first sample of 2 ml. The hematocrit should be as expected (i.e. about 75-80% of the target hematocrit) Correct the total amount of blood if the hematocrit is too high or too low according to the expected value.
- When 100% of blood has been infused, check again following same steps as above.
- Special situation: Cases of severe anemia with fetal hydrops. Transfuse 50% of the blood intravenously and the other 50% intraperitoneally, to reduce the risk of fetal hemodynamic decompensation and death. Schedule a new transfusion within 5-7 days.
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2.2. Intravenous drug administration

The procedure is the same as for cordocentesis with the injection of the drug once the umbilical vein has been cannulated. The fetal heart rate should be monitored during the procedure.

The indications are today essentially limited to intravenous treatment with Amiodarone, Digoxin or Flecainide in cases of fetal tachyarrhythmia with hydrops that does not respond to transplacental treatment (see specific protocol).

2.3. Complications

See section 1.3.

2.4. Post-procedure follow-up

See section 1.4.