Leids Universitair
Medisch Centrum

RESEARCH PROPOSAL

Unraveling the neurodevelopmental deficit in TAPS donors – what is the role of hypoxia and hypoglycemia?

Monochorionic twins share one placenta during pregnancy and have their blood circulation connected to each other via vascular anastomoses at the placental surface. Under normal circumstances, the blood flow between the two fetuses is equal. However, in approximately 15% of monochorionic twin pregnancies, there is a distorted balance in blood distribution. The most well-known form of unbalanced transfusion in monochorionic twins is twin-twin transfusion syndrome (TTTS), a condition that develops in 10% of monochorionic twin pregnancies(1). In TTTS, transfusion of large volume of blood from the one twin (the donor) to the other twin (the recipient) through relatively large placental anastomoses leads to hypovolemia and oliguria in the donor twin, and hypervolemia and polyuria in the recipient twin. This situation gradually results in shortness of amniotic fluid (oligohydramnios) in the donor twin and an excess of amniotic fluid (polyhydramnios) in the recipient twin. The best treatment for TTTS is fetoscopic laser surgery, an endoscopic intervention during which the placental vascular connections are coagulated, thereby artificially separating the fetal circulations.

Twin anemia polycythemia sequence (TAPS) is a relatively new form of unbalanced transfusion in monochorionic twins. The term TAPS, as well as the pathophysiological mechanism behind the condition, was first described by our research group in Leiden, the Netherlands(2). We have showed that TAPS occurs as the result of slow, chronic transfusion through minuscule placental anastomoses, causing the donor twin to gradually become anemic and the recipient twin to become polycythemic. In contrast to TTTS, TAPS develops in the absence of amniotic fluid discordances. At birth, TAPS typically presents with a pale anemic donor twin and a plethoric red recipient twin. TAPS can occur spontaneously in up to 5% of monochorionic twins (spontaneous TAPS)(3, 4), or can develop in 2-16% of TTTS twins treated with laser surgery, due to the presence of minuscule residual anastomoses (post-laser TAPS)(5, 6). Fetal demise occurs in up to 10% of TAPS twins, with donor twins being at increased risk for mortality(7, 8). Short-term neonatal outcome in TAPS varies between isolated hematological complications to severe cerebral injury in 3-11% and even neonatal death in 4-10%(7, 8). Currently, the best treatment for TAPS is unknown. Options include expectant management, preterm delivery, intrauterine transfusion in the donor twin (combined with a intrauterine partial exchange transfusion in the recipient twin), fetoscopic laser surgery and selective reduction. The most optimal treatment is currently investigated in the TAPS trial.

Recently, our research group also published on the long-term outcome after spontaneous TAPS. We showed that severe neurodevelopmental impairment (NDI) was found in 9% of TAPS survivors(9). Surprisingly, there was a striking difference in NDI between TAPS donors (18%) and TAPS recipients (only 3%). Compared to recipients, TAPS donors showed higher rates of cognitive impairment (18% vs. 41%, resp.) and bilateral deafness (0% vs. 15%, resp.). The cause of the increased rate of NDI and deafness in TAPS donors is not known.

Notably, this high rate of deafness is not reported in TTTS survivors nor in children that suffered from severe fetal anemia due to other caused such as red blood cell alloimmunization (Rhesus disease). Deafness in TAPS donors was based on auditory neuropathy spectrum disorder (ANSD), a type of sensorineural hearing loss in which the cochlea is unaffected but the cerebral structures responsible for the conduction of sound to the brain stem (such as inner hair cells or auditory nerve) is damaged.

The increased rate of both cognitive impairment and sensorineural deafness in TAPS donors may theoretically be related to chronic intrauterine hypoxia. We hypothesize that the chronic anemic state of the donor might have led to an hypoxic environment, gradually damaging the developing brain and the auditory nerve system. When limited levels of oxygen are available, the human body shifts to anaerobic glycolysis, a process in which glucose is transformed to lactic acid to ensure the body of enough energy. High levels of lactate acid in the donor twin will lead to fetal acidosis (a lowered pH value), a condition that is associated with cerebral injury, and long-term severe sequalae. According to our theory, TAPS donors might present with lower pH values and higher lactate values on day one after birth. Chronic fetal hypoxia, lactate acidosis and anemia can also lead to a severe condition at birth termed persistent pulmonary hypertension of the newborn (PPHN). Prompt recognition and treatment at birth with adequate respiratory and circulatory support using nitric oxide is of paramount importance. Delay in the management of PPHN may lead to further deterioration and irreversible damage due to persistent hypoxic injury, and further aggravate cerebral injury.

Alternatively, severe neonatal hypoglycemia might also explain the increased risk of NDI in TAPS donor twins. We recently noted at our neonatology department that TAPS donors appear to have severe hypoglycemia directly at birth. Glucose is an essential nutrient for the functioning of the human body, especially the brain. TAPS donors might have depleted glucose and glycogen storages due to chronic loss into the recipients' circulation, or due to increased use as a result of chronic hypoxia. Illustratively, 50% of TAPS donors are severely growth restricted(8). In general, infants that experience severe hypoglycemic episodes requiring treatment within the first few days of life have a higher chance of developing neurological or neurodevelopmental damage than normoglycemic infants. Untreated or severe neonatal hypoglycemia may cause irreversible damage to both the posterior occipital and cortex regions of the brain, two areas that are known to be crucial for cognitive functioning. If our hypothesis turns to be true, and TAPS donors are frequently hypoglycemic at birth, prompt neonatal treatment in TAPS donors could be extended with glucose intravenous infusion directly after birth, followed by a high caloric intake at the NICU if indicated.

Objectives of our research

- To retrospectively investigate the prevalence of neonatal acidosis and PPHN in TAPS donors compared to TAPS recipients
- To retrospectively investigate the prevalence of neonatal hypoglycemia in TAPS donors compared to TAPS recipients

Time table

Task	Time needed (research position for a post-doc 1 day a week)
Writing research protocol	1 month
Submitting the protocol, and getting approval from the departments' Science Committee and the Medical Research Ethics Committee	2 months
Data collection	3 months
Data analysis	3 months
Writing the manuscripts	3 months
TOTAL	12 months

Funding

Researcher type	Post-doctoral researcher (L. Tollenaar)
Work schedule	Part-time; one day a week
Yearly costs	€10.000

References

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