Objective
We report case of a patient referred to our fetal medicine center in the 37th week of her second pregnancy for unclear ultrasound findings in the central nervous system with suspicion of hydrocephalus. We aim summarise prenatal care and perinatal outcome of a fetus with non-syndromic semilobar holoprosencephaly.

Methods
The patient is a para 1, who had an uncomplicated vaginal delivery at term five years ago. There were no significant family history, with the absence of genetic risk factors. The patient was treated for a schizoaffective disorder with quetiapine and sertraline. During the pregnancy, methyldopa and metoprolol were added in the 22nd week, after the development of gestational hypertension. The patient did not undergo the first trimester screening, only the triple test was performed with a positive result (1: 18 for trisomy 18) and further evaluation (including both invasive and non-invasive procedures) was refused by the patient. Fetal anomaly scan in the second trimester was not performed by an experienced sonographer, only fetal biometry was documented. Multiple abnormalities were shown during the ultrasound examination performed in the 37th week of pregnancy after referral to our center. Ultrasound of the brain showed images of semilobar or nearly alobar holoprosencephaly (HPE) and cerebellar hypoplasia. Other ultrasound findings were agenesis of the right kidney and oligohydramnios. Normal facial and heart anatomy were described and no other abnormalities were shown. Estimated fetal weight was 2330g (corresponds to 5th percentile) and normal values were recorded by Doppler assessment (pulsatility index of umbilical artery 0.9). A caesarean section was performed in the 38th week of pregnancy for maternal request after patient refusal of vaginal delivery, despite being repeatedly informed about disadvantages of such approach. Surgery was uneventful, only green-stained amniotic fluid was noted. The birth weight of the female newborn was 2350g. Intubation was necessary already in the delivery room due to the inadequate respiratory activity, with Apgar score of 5/5/6. General hypotonia, mild hypertelorism (while hypotelorism is more common in HPE), low-set ears and anteriorly displaced anus were described on physical examination. Postnatal MRI and ultrasound examinations confirmed the diagnosis of semilobar HPE, cerebellar hypoplasia and agenesis of the right kidney. No heart defects were detected on the echocardiography. On the 3rd day after birth, due to the life-limiting prognosis, respiratory support was withdrawn followed by neonatal death. Genetic testing using QF-PCR analysis ruled out aneuploidy of chromosomes 13, 18, 21, X and Y, and no mutations were detected in genes associated with HPE (namely genes SHH, ZIC2, SIX3 and TGIF1) by molecular genetic testing. As there are many other causes of HPE, only those mentioned above were ruled out so far. Nonsyndromic HPE was the conclusion of genetic examination.

Results
According to the literature, the incidence of HPE is 1 in 10000-15000 births. HPE is a complex abnormality of the forebrain – incomplete separation of cerebral hemispheres with different degrees of abnormal cerebral architecture. No precise boundaries between the three types of HPE (alobar, semilobar and lobar) are defined. Ultrasound examination shows one single ventricle, a large dorsal cyst and no visible midline structures. The diagnosis can be established already during the first trimester screening or during the ultrasound anomaly scan in the second trimester. The etiology of HPE is heterogeneous. Identified causes include chromosomal abnormalities (e.g. trisomy 13), various syndromes (dominant, recessive, X-linked), environmental factors (e.g. exposition to retinoic acid, salicylates, anticonvulsants, cytomegalovirus, rubella and toxoplasma infection) and others. Differential diagnosis includes hydranencephaly, large cysts and severe hydrocephalus. Overall prognosis of HPE is very poor, especially in severe cases. The patient in our case had neglected her prenatal care, which led to a very late diagnosis of HPE. It can be assumed that if the ultrasound screening in the first and second trimester had been performed in an appropriate manner, fetal malformation would have been clearly visible and termination of pregnancy would have been proposed. Another issue in this case is delivery by a caesarean section which was not indicated by the obstetrician but necessary due to the recommendation of psychiatrist for the maternal request.

Conclusion
Holoprosencephaly is a rare disorder of brain development with a very poor prognosis, which can be diagnosed in the first or second trimester if the ultrasound examinations are performed properly.