Recurrent cerebral ischaemia in a pregnant woman with patent foramen ovale II° and thrombophilia

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Summary
This case report concerns a pregnant multipara (age: 27 years) in the 16th gestational week. She developed a sudden onset of paraesthesia in her left lower arm although injecting dalteparin 5000 IU once daily subcutaneously (s.c.) due to a heterozygous factor V Leiden mutation and a prior miscarriage in the first pregnancy and preeclampsia in her third pregnancy. After the miscarriage she delivered two healthy children under prophylactic anticoagulation with low molecular weight heparin (LMWH). Now via magnetic resonance imaging (MRI) she was diagnosed as having multiple cerebral ischaemic lesions. Further workup revealed the presence of a patent foramen ovale (PFO) II° but no venous thrombosis in her legs. She was then treated with dalteparin 5000 IU twice daily by subcutaneous injections. At 19th gestational week she developed paraesthesia in her left lower arm again. The MRI showed a cortical lesion in the territory of the right median cerebral artery. The anticoagulation dose was increased stepwise under surveillance of the anti-FXa-level 3–4 h after subcutaneous injections aiming to achieve the supratherapeutic range of 1.2–1.5 IU/ml anti-Xa-units. No more neurological symptoms appeared under this antithrombotic therapy. The patient delivered by induction of labor at the 38th gestational week.

Schlüsselwörter
Pregnancy, recurrent stroke, thrombophilia, PFO

Zusammenfassung
Eine 27-jährige Schwangere in der sechzehnten Schwangerschaftswoche entwickelte plötzlich eine Parästhesie im linken Unterarm, obwohl sie seit Beginn der Schwangerschaft Dalteparin 5000 IU einmal täglich subkutan applizierte wegen einer heterozygoten Faktor-V-Leiden-Mutation. Mittels Ultraschall wurde ein offenes Foramen ovale (PFO) II° diagnostiziert, eine Beckenbeinvenenthrombose wurde ausgeschlossen. Aufgrund des Ereignisses wurde die Dosis der Antikoagulation auf Dalteparin 5000 IU zweimal täglich erhöht.


Pregnancy-associated stroke is rare, but its impact on mortality and morbidity of women is considerable. Recent data from the United Kingdom show the incidence of stroke in pregnancy has risen, probably due to increasing maternal age. Women with concomitant diagnosis of hypertension and heart disease have an increased risk for ischaemic and haemorrhagic stroke (1).

Stroke accounts for approximately 12% of maternal deaths and contributes to significant fetal morbidity and mortality (2).

Pregnant women develop stroke more frequently than non-pregnant women (incidence varies between 11 and 34 per 100 000 deliveries). 10 percent of pregnancy-associated strokes occur in the antepartum period, 40 percent around delivery and 50 percent postpartum (3).

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Cryptogenic strokes account for 30 to 40 percent of all ischemic strokes in both women and men. The TOAST classification defines the cryptogenic stroke as:
- brain infarction, which occurs without a reason for cardio embolism,
- large vessel atherosclerosis,
- small artery disease,
- incomplete diagnostic workup or with two or more possible reasons.

Currently, patients with less-well established possible causes such as PFO, valvular strands, antiphospholipid-syndrome, aortic arch arteroma and prothrombotic disorders are mostly classified in this subgroup.

Strokes in pregnancy are strongly and significantly associated with:
- Caesarean delivery,
- disorders of fluid, electrolytes and acid-base-system,
- hypertension,
- hypercoagulability due to maternal physiological changes,
- preeclampsia and eclampsia,
- paradoxical embolism,
- postpartum cerebral angiopathy and
- peripartum cardiomyopathy.

Rare causes for strokes in pregnancy are:
- Moyamoya-disease,
- antiphospholipid-antibodies,
- gestational throphoblastic disease,
- thrombotic thrombocytopenic purpura (9) and
- sickle cell disease.

Multiple gestations might also raise the risk.

Preeclampsia and eclampsia are the most common causes for ischemic and hemorrhagic strokes in pregnancy due to impairment of cerebrovascular autoregulation.

We are presenting a case of recurrent stroke during pregnancy despite therapeutic anticoagulation with low molecular weight heparin (LMWH).

**A woman with FV Leiden**

A pregnant multiparous woman (age: 27 years) was currently treated in our outpatient clinic due to pregnancy and heterozygous factor V Leiden mutation. With a height of 169 cm and a weight of 53 kg she had a body mass index (BMI) of 18.6 kg/m². The patient had never suffered from a thromboembolic event. The analysis for thrombophilia was done nine years ago as screening before starting with birth control pill. Her father had had a myocardial infarction at around 50 years of age. There was no familial history of venous thromboembolism. Four years ago an iron deficiency anaemia was diagnosed.

The patient suffered from a miscarriage in the 10th gestational week during her first pregnancy three years ago and was then treated in the following pregnancies with 5000 dalteparin once daily s.c. Under this treatment she delivered a healthy boy 30 months and a healthy girl 9 months ago.

Because of elevated liver enzymes due to preeclampsia the birth of the second child was induced. Six months after the birth of the second child she became pregnant again. In the 16th gestational week a paraesthesia in the left lower arm and a migraine-like headache occurred. The symptoms were fully abating during the next few hours. The patient was transferred to a hospital and the MRI showed multiple small cerebral ischemic lesions in the area of the right anterior cerebral artery despite uninterrupted treatment with dalteparin 5000 IU once daily (Fig. 1a).

We discussed several therapeutic options with the patient. The option of starting low dose acetylsalicylic acid (ASA) 100 mg once daily was suggested but refused by the patient. Therefore, the dalteparin dosage was elevated to 5000 IU twice daily at a bodyweight of 53 kg.

The long-term electrocardiogram showed a continuous sinus rhythm. The echocardiography detected a PFO II° with passover of contrast agent under Valsalva manoeuvre, as a potential cardioembolic source of the ischemic stroke, there was no atrial septal aneurysm. Per duplex ultrasound of the carotid and vertebral arteries as well as the intracranial vessels showed no pathologic

Fig. 1  MRI imaging of ischaemic lesions
a) 16th gestational week: first lesion in the area of the right anterior cerebral artery
b, c) 19th gestational week: second lesion in the right postcentral gyrus

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pattern. The results of an electroencephalogram were unremarkable.

Laboratory diagnostics revealed no pathological markers: leucocytes 8.64 x 10^9/l, haemoglobin 12.3 g/dl, thrombocytes 267 x 10^9/l, lipoprotein a 16 mg/dl. The values for CRP, electrolytes, liver enzymes, creatinine, urea and uric acid were within the reference range. Antinuclear antibodies, perinuclear and cytoplasmic antineutrophil cytoplasmic antibodies, antibodies against doublestranded DNA, anticardiolipin antibodies and lupus anticoagulant could not be detected either.

In the 19th gestational week the patient developed acute paraesthesias in the left lower arm again without other neurological pathologies. She was transferred to the Stroke Unit at the University Hospital of Mainz. A second MRI was carried out and revealed a new ischaemic lesion of 7 mm diameter in the Gyrus postcentralis which is supplied by the right median cerebral artery (Fig. 1b,c).

Laboratory diagnostics showed again no pathological markers: leucocytes 9.85 x 10^9/l, haemoglobin 12.2 g/dl, thrombocytes 267 x 10^9/l. The values for CRP, procalcitonin, electrolytes, liver enzymes, creatinine, urea and uric acid were all normal again. Again there were no pathological titers of antinuclear antibodies, perinuclear and cytoplasmic antineutrophil cytoplasmatic antibodies, antibodies against doublestranded DNA, anticardiolipin antibodies and lupus anticoagulant.

Further diagnostic revealed TSH 1.17 mU/l, INR 1.0, aPTT 35.5 s, fibrinogen 353 mg/dl, antithrombin 101%, plasminogen 123%, D-dimer 0.38 µg/l, homocystein 4.1 µg/l, factor VIII:C 181%, XI:C 88%, IX:C 94%, protein C activity 134%, protein S activity 50%, free protein S antigen 64 µg/l. The patient did not change the course of therapy in the following months. No new neurological pathology occurred and at time of delivery again a supratherapeutic dose of LMWH strictly monitored by anti-FXa-level with the aim of achieving 1.2–1.5 IU/ml 3–4 h after subcutaneous application, like the aim level for pregnant patients with prosthetic mitral valve. LMWH treatment was switched from dalteparin 5000 IU twice daily to enoxaparin 6000 IU twice daily, then increased to 7000 IU twice daily guided by anti-FXa-levels. This dose was kept until the induction of labour (Tab. 1).

Labour was induced at 38th gestational week due to elevation of liver enzymes, the history of mild preeclampsia and the current situation of recurrent strokes. With accentuation of labour we switched to dalteparin by continuous i.v.-infusion at 150 IU per hour based on our own experiences with this peripartum regimen. A healthy boy was delivered without any bleeding complications.

Postpartum, we increased dalteparin in a stepwise manner to 250 IU/h intravenously on the day of birth. On the first postpartum day we increased the dalteparin dosage further to dalteparin to 500 IU/h.

On the second day after delivery dalteparin i.v. was switched to enoxaparin 7000 IU twice daily as before delivery and then during the following days titrated by anti-FXa-levels to 5000 IU twice daily s.c. The patient did not change the course of therapy in the following months. No new neurological pathology occurred and at time of delivery she is nine months after delivery pregnant again in the 10th gestational week. This time she was initially persuaded to take acetylsalicylic acid 100 mg/day in combination with enoxaparin 5000 IU twice daily, but then decided against our suggestions to reduce the dosage to ASA 50 mg every second day for fear of bleeding complications. Up to now no new neurological pathologies occurred.

**Discussion**

Either a CT scan or a magnetic imaging of the cerebrum without contrast agent can be performed in a pregnant woman. As there is no radiation involved with MRI and it is the superior diagnostic tool, MRI is the preferable option. Cardioembolic cerebral infarcts are typically found in multiple foci that can be localized to different vascular territories. Several ischaemic insults within the same supplying cerebral artery rather indicate an origin from carotid or vertebral arterial sources.

The therapeutic options for this case were based on the recommendations for non-pregnant adults, since there a possibilities of antiplatelet or anticoagulation therapy that are widely used in pregnant patients as ASA or LMWH.

There are multiple indications for administering LMWH during pregnancy and postpartum period. Therapeutic doses are required for women who receive chronic oral anticoagulation or for women with a venous thromboembolism during the current pregnancy. Women with prosthetic heart valves are treated sometimes even with supratherapeutic doses (13). Therapeutic doses of LMWH heparin is based on the bodyweight and usually administered twice daily. Pregnancy associated weight gain and different metabolism, plasma volume and other physiological factors affect the bodyweight-administered dosing regimen and so it is widely recommended to test the anti-FXa-Level 3–4 hours after s.c. administration.

Intermediate or prophylactic dosing regimen is required for women at a risk for thrombosis, such as those who had VTE prior in history, with

<table>
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<tr>
<th>D-dimer (mg/l) cut-off &lt;50 mg/l</th>
<th>LMWH dose (IU)</th>
<th>gestational week</th>
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<tbody>
<tr>
<td>0.31</td>
<td>14000</td>
<td>19+4</td>
</tr>
<tr>
<td>0.35</td>
<td>14000</td>
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<tr>
<td>0.47</td>
<td>14000</td>
<td>31+5</td>
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<tr>
<td>0.47</td>
<td>14000</td>
<td>35+6</td>
</tr>
<tr>
<td>0.65</td>
<td>14000</td>
<td>38+0</td>
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<tr>
<td>1.40</td>
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<td>1.24</td>
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<td>&gt;0.2</td>
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• antiphospholipid-antibody syndrome (in combination with ASA 100 mg) or
• homozygous factor V Leiden mutation or prothrombin G20210A Mutation (14).

Women with lower risk thrombophilias and no prior VTE should be monitored closely and only receive prophylactic therapy in combination with other risk factors (e.g. immobility) (15).

The data for using LMWH anticoagulation in women with thrombophilic defects and recurrent pregnancy loss are less clear. The 2012 guidelines of the American College of chest physicians (ACCP) recommend against the use of antithrombotic prophylaxis with an evidence grade II C (15). For women with recurrent unexplained pregnancy loss the 2012 ACCP guidelines do not recommend treatment with LMWH with an evidence grade I B (15). However it is a common treatment for those patients throughout the world and more data are needed.

Prophylactic and intermediate LMWH dosing regimen does not require anti-FXa-level testing.

It is important to use preservative free single dose syringes, since alcohols, which are used as preservatives for multidose vials of LMWH can have adverse side effects on the fetus and thus are contraindicated in pregnancy.

The 2012 ACCP guidelines recommend antiplatelet therapy for patients with cryptogenic ischemic stroke and a PFO and state that anticoagulation is not indicated (16). The guidelines of the American Heart Association and the American Stroke Association (AHA/ASA) recommend antiplatelet therapy for patients with ischemic stroke or TIA and PFO. However, the latter guidelines also state that anticoagulation might be reasonable for high-risk patients with other conditions such as a hypercoagulable state and especially for patients with evidence of DVT. Antiplatelet therapy should then be started when anticoagulation is finished (17).

Our patient was treated after the first stroke with full therapeutic anticoagulation due to her several risk factors (thrombophilia, pregnancy, prior preeclampsia, PFO and stroke despite high-dose antithrombotic prophylaxis). Another option would have been the closure of the PFO which can be achieved percutaneously. However, due to the radiation levels percutaneous intervention is not a desirable option for a pregnant woman. Of course the fetus is not in the direct path of X-ray, but there is still the risk of secondary radiation. If complications during the implantation of the occluder occur, then this could lead to an open thoracotomy.

Furthermore, the efficacy of closure of a PFO on the rate of recurrent stroke has not been established. Three randomized controlled trials (Closure I, PC and Respect) indicate that device closure of a PFO does not offer significant benefit over medical therapy alone for prevention of recurrent stroke (18–20). A reason for this could be, at least in part, the small associated absolute risk. Secondly, a high proportion of recurrent cerebral ischaemic events are not directly related to a paradoxical embolization.

As our patient refused to take ASA in combination with a therapeutic anticoagulation we decided for a supratherapeutic dose of LMWH with a target anti-FXa-level between 1.2 and 1.5 IU/ml, the usual way we treat pregnant women with mechanical mitral valves, who have the highest risk for cardioembolic events during pregnancy.

We established in our center an even higher target level than suggested in the guidelines from the European Society of Cardiology 2011 for those patients (13).

Luckily, the neurological symptoms in our patient fully regressed after several hours, so we did not have to evaluate systemic fibrinolytic therapy. There are only very few case reports of successful administration of recombinant tissue-type plasminogen activator (rt-PA) on pregnant women (21).

For delivery we switched to dalteparin by continuous i.v.-infusion at 150 IU per hour based on our own experiences with this peripartum regimen. I.v.-infusion of dalteparin is an off-label use. Nevertheless, we have experiences on several thousand patients in the preceding two decades in our center. It can be monitored by anti-FXa-testing. The advantage in comparison to unfractioned heparin via i.v.- infusion is that a stable anti-Xa-level is reached much faster. When infusion is stopped due to bleeding complications, the anticoagulatory effect passes equally fast (22).

Conclusion

This case presents an otherwise healthy woman with recurrent cryptogenic ischaemic insults during the course of pregnancy with a small PFO and heterozygous factor V Leiden mutation. The second episode took place under correct body weight adapted therapeutic anticoagulation with LMWH. Using a supratherapeutic dosage with LMWH no more incidents occurred.

Because the number of pregnant women with strokes increases, clear solutions for treatment are urgently needed.

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Conflict of interest

The authors declare that there are no conflicts of interest.

References

7. Ros HS, Lichtenstein P, Bellocco R et al. Pulmonary embolism and stroke in relation to pregnancy: