

Management of unruptured brain aneurysms during pregnancy and puerperium

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ABSTRACT

Aneurysms are sac-like dilatations of weakened wall areas within blood vessels. Cardiovascular related issues, such as hypertension, can put one at risk of developing such complications, with the possibility of rupturing. In the case of intracranial aneurysms, an outpouching forms where there is turbulent blood flow, often at the bifurcation of arteries. Depending on the morphology and location, different treatments need to be considered, but during pregnancy, further physiological changes also factor into decision making. In pregnant patients, intracranial hemorrhage cases are relatively low, yet they cause a high mortality rate amongst women, hence early detection and management of unruptured aneurysms is of significant importance.

Keywords: aneurysm, pregnancy, puerperium

INTRODUCTION

During pregnancy, women experience changes in physiological parameters. Different associated pathologies, such as pregnancy-related hypertension, can constitute factors leading to or aggravating an aneurysm, making the gestational period more difficult to manage, in no small part due to lack of screening and treatment guidelines [1]. Data regarding management of unruptured aneurysms during pregnancy are still scarce. The purpose of this article is to select and review the existing literature to convey management strategies for this pathology in pregnant patients. Screening for aneurysms and ensuring proper treatment during gestation helps avoid the negative consequences of rupture during pregnancy, labour or puerperium.

EPIDEMIOLOGY

The female sex is a significant risk factor in aneurysm formation (out of 4060 patients evaluated by the International Study of Intracranial Unruptured Aneurysms 75% being women) [2], especially during pregnancy, puerperium and menopause during which more risk factors are encountered. Although it appears in 3-11 in 100.000 of pregnancies, intracranial hemorrhage causes around 35% of maternal and 17% of fetal deaths [1]. The likelihood of rupturing increases significantly in the third semester of gestation and the following 6 weeks of post-partum [2]. Hence, it is of critical importance for the clinician to properly assess patients with suggestive symptoms and detect an aneurysm on time, while not misdiagnosing the patient and unnecessarily ex-

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posing her or the fetus to contrast substances or radiation.

As some data suggests, late pregnancy and puerperium particularly show an increase in risk of aneurysmal rupture, pointing to a need for more urgent care. S. J. Kittner et al. concluded that it is more likely for subarachnoid hemorrhage (SAH) to occur in the first six weeks of post-partum rather than during pregnancy [3]. Their study evaluated female patients aged 15 to 44, diagnosed with cerebral infarction and intracranial hemorrhage (ICH) and showed a 5.6 times higher chance of ICH affecting the subgroup of patients who were pregnant or up to 6 weeks post-partum [3].

PATHOPHYSIOLOGY

Hemodynamic and cardiovascular changes, such as an increase in plasma volume by 30-40% (and as a result in total blood volume by 45% and by up to 60% by the late third semester), higher levels of erythropoietin, red and white blood cell counts normally occur during gestation. An apparent hemodilution is to be expected due to higher liquid retention (while the mean corpuscular volume and mean corpuscular hemoglobin concentration remain within normal limits). Ultimately, there is an increase in fibrinogen (by up to 50%) and clotting factors (mainly VIII, IX and X) during pregnancy, in anticipation for the hemostasis required during labour and delivery [2]. Thus, the balance of coagulation shifts due to anticipation of hemorrhage during labour, favouring clot formation.

Other significant changes concerning the cardiovascular system are an increase in cardiac output (by 20% at 8 weeks gestation and by 60% - the maximum elevation - between 20-28 weeks) and vasodilation of peripheral blood vessels which decreases vascular resistance (by 25-30%), both representing risk factors in aneurysm formation and rupture [2].

Likewise, hormonal changes also accentuate these effects, as progesterone, human chorionic gonadotropin are all present in high levels in pregnancy and contribute towards decreased vascular resistance [1], possibly leading to intracranial aneurysm formation, enlargement and rupture. The role of estrogen is still controversial, as some studies state it contributes to this effect [1], while others consider it to rather have a protective role over the cardiovascular system, as its deficiency was shown to lead to inflammation of endothelium, rupture and SAH [3].

Lower vascular resistance during pregnancy stimulates the renin-angiotensin-aldosterone (RAA) system, leading to a three-fold elevation in aldosterone secretion in the first semester and a ten-fold one in the third semester. Angiotensin II increases two-

to four-fold and renin three- to four-fold compared to values of non-pregnant women [4]. These changes bring about saline retention, with an increase in plasma volume, blood pressure and vasoconstriction.

During delivery, cardiac output increases significantly (by 15% in the first stage of labour and 50% in its second stage), sympathetic stimulation elevates heart rate and blood pressure as a response to pain and anxiety and uterine contractions determine a release of 300-500 ml of blood into the systemic circulation [4]. Further physiological changes take place after birth, as the inferior vena cava is decompressed by the uterus reducing its dimensions. This leads to an increase of 60-80% in cardiac output, which returns to pre-labour values within hours after this extreme effect [4]. These events can negatively impact patients with intracranial aneurysms and cause SAH.

The physiological changes that happen during pregnancy are normal and meant to accommodate the needs of the developing fetus. However, they can bring about higher risks of aneurysm formation and subsequent rupture.

SAFE INVESTIGATIONS AND DIAGNOSIS

Due to the potentially harmful effect of the ionizing radiation on the developing fetus, computed tomography (CT) and digital subtraction angiography (DSA) need to be used with greater care. The contrast substances can lead to abnormal development during all stages of pregnancy [5], however shielding of the fetus is a useful method of still employing these, if needed. Shielding of the patient's abdomen using a double lead apron during imaging is a commonplace practice, as it exposes the fetus to less radiation. The usual dose received by the fetus is between 1-5 mGy, below the recommended limits established by the United States Nuclear Regulation Commission (USNRC) and the Center for Disease Control (CDC). They recommend total exposure of the fetus to be less than 5.0 mSv (500 mrem). Doses below 50 mGy are deemed safe, the effects of radiation doses between 50 mGy to 100 mGy were deemed inconclusive on fetal development by the CDC, while those above 100 mGy (especially above 150 mGy) are considered the minimum at which negative outcomes for the fetus will occur [2]. A body phantom study included in the paper of Ishii et al. classifies different degrees of safe radiation exposure relative to gestational age, the threshold for the first gestational week being 100 mGy for the period between 2-8 weeks 500 mGy, between 8-15 weeks 120 mGy, between 16-25 weeks 250 mGy and for more than 25 weeks the threshold is 500 mGy [5].

The American College of Radiology assessed magnetic resonance angiography (MRA) to be a safe

alternative for all stages of pregnancy [2]. Gadolinium is a contrast agent commonly used. Although Nussbaum et al. assert in their systematic review that this substance is safe despite crossing the placental barrier, other studies state that gadolinium has a relatively long half-life and it can have negative effects on fetal growth [1]. Ishii et al. reference its teratogenic effects from conducted animal studies and argue against contrast enhanced MRA unless the necessity to do so outweighs the risk to the fetus [6]. Other sources recommend limited exposure to it, arguing for insufficient evidence into gadolinium's effect on the fetus and taking into consideration the fact that due to its long half-life it remains in the fetal circulation (and after excretion in the amniotic fluid) [3].

The conundrum of finding an appropriate way of screening has not yet been concluded, as different sources argue differently for the use of gadolinium. As with most other aspects of pregnancy-related care, a collective effort between several medical specialties (obstetrics, neurosurgery and radiology) needs to be present for the best outcome.

SCREENING CRITERIA

Kataoka et al. defined a list of seven risk factors linked to aneurysm formation which should be considered for triaging patients considered high-risk in the pregnant population for imaging. The criteria are as follows: past history of cardiovascular disease (CVD), age ≥ 40 years old, parents with history of CVD, chronic hypertension ($\leq 160/110$ mmHg), pregnancy-induced hypertension, chronic headache and obesity (defined as body mass index ≥ 25 kg/m²) [7].

Other aspects that need to be factored in when suspecting the presence of an unruptured aneurysm are conditions like polycystic kidney disease (in family or personal history), Marfan syndrome, Ehlers Danlos syndrome (as well as other conditions that affect the integrity of blood vessels), headaches and neurological deficit [1].

GRADING SYSTEMS AND RISK ASSESSMENT

Aneurysms are classified with regard to their type (saccular, fusiform, mycotic), size (small <11 mm, large 11-25 mm, giant >25 mm in diameter). Another important aspect relating to morphology is the dome to neck ratio, as wider necks are more difficult to clip, while large domes might require prior shrinking or opening in the eventuality of containing thrombi. Intracranial aneurysms are most often saccular (berry) shaped and are located deep within the brain (at its base), at branching points of the circle of Willis. Giant aneurysms may compress structures adjacent to them, producing specific signs and symptoms [2].

There are several grading systems for assessing the severity of aneurysms, all of which classify unruptured aneurysms as grade 0, while higher grades are used to communicate presence of SAH and the extent at which it affected surrounding structures [8]. The Hunt and Hess grading system is used for relating outcome of a cerebrovascular accident (CVA) and it has grades from 0 to 5 (5 being the most severe condition) [9]. Similarly, the Yasargil classification uses a scale from 0 to V and it uses the subcategories of b and a to communicate the appearance of a focal neurological deficit (an abnormal function of a particular body area due to injury to the nervous system) or the situation when it is not apparent, respectively. For unruptured aneurysms, grade 0a describes no neurological deficit and 0b points to deficits such as cranial nerve III palsy, chiasma syndrome, progressive hemisindrome (for giant aneurysms) [8]. Due to considerable room for interpretation between physicians when using the already mentioned systems, the World Federation of Neurosurgical Societies' committee created a scale based on the Glasgow Coma Scale (GCS) in which unruptured aneurysms are given grade 0 (not corresponding to a score on the GCS) out of a maximum of 5 (corresponding to a 3-6 on the GCS) [2].

MANAGEMENT

Nussbaum et al. [1] consider that an appropriate way of managing an unruptured aneurysm is taking into consideration its size. Patients with small aneurysms should be closely monitored using MRA along the pregnancy, while those with large aneurysms or with observed enlargement should get treated. The study affirms that clipping and coil embolization are both safe and efficient in pregnancy, however the former requires longer hospital stays and the latter administration of anticoagulants and exposure to radiation. Heparin is unable to cross the placenta and is deemed safe for the fetus, but a higher concentration is required due to the balance within the coagulation system shifting towards clotting [1]. Consequently, the mother would be exposed to a higher risk of hemorrhage in the eventuality of requiring a C-section. The radiation from the DSA is minimal and the fetus can be shielded by a double lead apron placed on the mother's lower abdomen.

A recent case report by R. Pop et al. [10] describes what they consider to be the first reported treatment of an unruptured aneurysm with flow diverter stent. A 41-year-old patient presented with a giant unruptured carotid-ophthalmic aneurysm (21.5 mm) in the twelfth week of pregnancy. Initially, the woman was given clopidogrel, but routine testing revealed resistance to the anticoagulant, so it was replaced with prasugrel and aspirin. During the 17th gestational week coiling embolization was per-

formed (given the location of the aneurysm), however due to residual filling the surgical team decided to introduce a flow diverter stent to avoid complications. None were reported during the coiling or post-intervention. The magnitude of the radiation did not go over 5 mGy, and after delivery at 39 weeks the infant did not show abnormalities [10].

Both large and small aneurysms ought to be treated through the aforementioned methods, as well as through administering anticoagulants. Aspirin is used in pregnancy to prevent pre-eclampsia and it does not raise risks of hemorrhage [11]. Clopidogrel seem to have no risks of teratogenic effects in fetuses, but literature data are still scarce [12]. Ticagrelor had negative effects when tested on animals, causing fetal growth retardation [13]. Prasugrel showed no teratogenic influence on fetal growth and several case reports show it is safe in combination with aspirin for administration in pregnancy [14].

CONSIDERATIONS FOR DELIVERY

Due to rare occurrence of aneurysms in pregnancy, the appropriate method of delivery should be decided on a case-by-case basis and requires multi-disciplinary collaborative work between obstetrics, neurosurgery, anesthesiology and radiology. C-sections are often performed so as to avoid the sudden rise in blood pressure during labour, which can cause the aneurysm to rupture, being the preferred method of assisting birth. However, patients with very small aneurysms can choose to undergo vaginal delivery if they wish to, while being informed of the dangers of continuous high blood pressure during labour and of the possibility that a C-section might be eventually necessary [1]. The duration of labour needs to be taken into consideration in this case, as L. T. Nyfløt et al. determined in a study showing an association between this variable (including active labour) and severe postpartum hemorrhage compared to the control group (5.4 and 3.8 hours, respectively) [15]. A C-section should thus be employed in this patient population before the 6-hour mark, as not doing so significantly raises the risk of severe post-partum hemorrhage [1].

Treating the aneurysm before or after birth is also a decision that would differ from patient to patient, depending on whether it is more important to have less fetal exposure to radiation and anesthetics, or whether the mother's health becomes of higher priority. More often than not, however, the safest option is to deal with the aneurysm as soon after its detection, by documenting its evolution in the case of patients with small aneurysms and by treating those with large ones surgically or through embolization [1].

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PUERPERIUM

An article by Kanani et al. [16] reveals the higher risk for ICH in pregnant patients and 6 weeks post-partum and analyses the outcome of a 37-year-old multiparous woman's case, stressing the importance of physiological changes during the puerperium and suggests the need for more immediate treatment in similar situations. After undergoing a C-section, the patient suffered from a seizure upon waking up from anesthesia. Due to negative development, with tonic posture, rolling back of the eyes, loss of consciousness and foaming at the mouth, she was intubated. Shortly after, the tonic posture ceased. Her pupils were reactive to light. A head CT showed a hypopattenuated (brighter) area in the left frontal lobe, suggesting an infarct, but no signs of hemorrhage were observed. The patient remained intubated in the ICU and was administered a propofol infusion. Later, she regained consciousness and upon examination did not show neurological deficits. The medical team arranged for a head MRI, done days later, which revealed the presence of a giant unruptured aneurysm (2,3 x 2,1 x 1,9 cm) of the left internal carotid pressing on the frontal lobe. She was scheduled for a follow up in four weeks, medical staff respecting routine procedure and not treating a puerperium case differently due to lack of guidelines surrounding it. The day after discharge she presented to the ER with severe headache. Her GCS was 15. Another seizure followed and after intubation another CT scan was run, uncovering SAH extending to the basal cistern and fourth ventricle. In consequence, all brain stem reflexes (besides the respiratory one) were lost. She died three days later, postmortem examination concluding the cause of death to be SAH [16].

As the prospect of ICH is suggested to be higher in female patients during puerperium, the finding of an aneurysm upon screening requires faster intervention [16].

CONCLUSIONS

Aneurysmal rupture during pregnancy is a significant cause for maternal and fetal mortality. As underlined previously, physiological changes lead to a greater vulnerability of pregnant and post-partum patients when it comes to unattended intracranial aneurysms. Despite more research being required to fully understand certain aspects of unruptured aneurysm management (such as imaging, the effects of anticoagulants on pregnant women and on fetal development), a step forward should be making populations at higher risk of rupture (women up to 6 weeks post-partum) a higher priority, especially when morphology and location of the outpouching is significantly affecting surrounding structures.

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