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# Pathophysiology of meningioma growth in pregnancy

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**Abstract:** Meningioma is among the most frequent brain tumours predominantly affecting elderly women. Epidemiological studies have shown that at the age of fertility the incidence is relatively low. The biological behaviour of meningioma in pregnancy is different from other meningiomas. The possible explanation is rooted in the complex physiological changes and hormonal differences during pregnancy. The increased meningioma growth observed in pregnancy is presumably the result of endocrine mechanisms. These include increase in progesterone, human placental lactogen (hPL) and prolactin (PRL) serum levels. In contrast, levels of pituitary hormones such as follicle stimulating hormone (FSH), luteinizing hormone (LH) and human chorionic gonadotropin (hCG) produced by the placenta are decreasing in the mother prior to childbirth. Besides, vascular factors also play a crucial role. Peritumoral brain edema (PTBE), with well-known causative association with vascular endothelial growth factor (VEGF), can often be seen both with imaging and in the surgical specimens. Our aim is to assess published research on this topic including diagnostic and therapeutic guidelines, and to provide a clinically useful overview on the pathophysiology and biological behaviour of this rare complication of pregnancy.

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## Abbreviations

CT - computed tomography

ER - estrogen receptor

FSH - follicle stimulating hormone

hCG - human chorionic gonadotropin

hPL - human placental lactogen

LH - luteinizing hormone

MRI - magnetic resonance imaging

NF2 - neurofibromatosis type 2

PR - progesterone receptor

PRL - prolactin

PTBE - peritumoral brain edema

VEGF - vascular endothelial growth factor

WHO - World Health Organization

## 1 Introduction

Meningiomas are responsible for more than one third of all intracranial tumours. They are more frequent in women, the ratio of female to male is 3:2. Primarily the elderly aged 60 -70 are affected. Meningioma has been first described by Harvey Cushing in 1922 and he was the first to name these tumours meningiomas [1]. Despite the high incidence of meningioma, the pathophysiology has not been fully understood [2]. Regarding genetic background, meningiomas could be a part of a familial tumour syndrome, most frequently associated with Neurofibromatosis type 2 (NF2) with NF2 gene mutation [3]. The gene is coding the tumour suppressor protein merlin, which has mutations in up to 60% of sporadic cases [4]. With recent advance of genetic research, the epigenetic background of meningioma pathogenesis has been elucidated in some details [5]. The aberrant DNA methylation affects numerous promoters and homeobox genes in meningiomas. Although, the role of histone modification has not been proven, changes in microRNAs regulating post translational silencing increase the chance of recurrence. Important environmen-

tal factor is the irradiation on the head and neck region. Meningiomas are frequent in survivors of nuclear disasters and there is an increased incidence of these tumours in patients who have had iatrogenic diagnostic or therapeutic irradiation [6]. With the increasing use of telecommunication technologies, including mobile phones, an association between meningioma pathogenesis and electromagnetic wave has been suggested. Although no significant and proven relationship has been established between the use of cell phones and meningioma development, it should be taken account that in these studies the follow-up time is relatively short [7]. Head injury has also been proposed and in some studies proven as a causative factor for meningioma development [8]. A comprehensive epidemiological study has established relationship between smoking and occupational exposure to heavy metals. In contrast, food rich in fresh vegetables and fruit appears to be protective [9]. There has been no statistically proven link between alcohol consumption and carcinogenesis [10]. The diagnosis of meningioma requires imaging techniques, either Computed Tomography (CT) or Magnetic Resonance Imaging (MRI). There are characteristic imaging features, dural tail, peritumoral brain edema (PTBE) and calcification on CT which are important additional clues to establish the diagnosis [11]. Clinical signs during tumour growth are caused by the space occupying and compressive effect of the tumours upon the underlying central nervous system structures. Therefore, even histologically benign tumours could prove clinically unfavourable or even lethal. Histological grading of tumour is based on the most recent World Health Organization Classification of Tumors of the Central Nervous System classification of meningioma (2016) [12]. Within the three grades (WHO grade I, II, III) 15 histological subtypes can be differentiated. WHO grade I tumours are meningothelial, microcystic, fibrous, secretory, transitional, lymphoplasmacyte-rich, psammomatous, metaplastic and angiomatous. WHO grade II tumours are chordoid, clear cell and atypical meningiomas with the presence of brain invasion, while WHO grade III tumours are papillary, rhabdoid and anaplastic meningiomas (irrespective of brain invasion). The WHO grade has a very important and comparatively accurate prognostic role. The chance of meningioma recurrence in WHO grade I, II, III ranges between 7-25%; 29-52%; 53-94% respectively. Beside the most frequent types there are rare meningioma variants; as an example, we refer to our case report of a 72-years old woman [13]. For better understanding the pathophysiology and risk of recurrence, simple neuropathological diagnostic methods like immunohistochemistry can be helpful. Such studies shed light to prognostic protein

markers involved in carcinogenesis and progression [14]. The analysis of invasion-related molecules has revealed important findings regarding recurrence in malignant gliomas [14-15], which might be implicated also in meningiomas, although the infiltrative potential in gliomas is characteristically much higher. Certainly, meningiomas are far less invasive tumours; nevertheless, the analysis of factors implicated in invasive growth and therefore increased risk of recurrence could improve our understanding of the underlying pathophysiology of meningioma recurrence.

Meningiomas rarely develop over the course of pregnancy. It is estimated that there are 5,6 cases out of 100.000 pregnancies [16]. One of the reasons for the low incidence is the fact that the range of fertility is approximately 15-45 years of age and during this time tumours in general are relatively low in frequency. This is also true for meningiomas, which have highest incidence between the ages of 60 and 70. The first literature report on a brain tumour in a pregnant woman was published by Barnard in 1898 [17]. A case report by Cushing and Eisenhardt on a pregnant woman with parasellar meningioma was issued in 1929. They reported rapid progression of visual impairment, which appeared reversible post-partum and recurred in the next pregnancy [18]. One important aspect of meningioma in pregnancy is the potentially rapid growth with life-threatening complications [19]. Owing to its localisation it can have a distribution similar to meningioma in the non-pregnant population. Meningiomas close to the skull base have special clinical relevance because they cause severe complications more frequently with the increased intracranial pressure [20]. In such cases the initiation of the adequate or available therapy is mandatory because a delay could cause life-threatening complication both to the foetus and the mother. The primary goal of the therapy is to save lives, which requires the close collaboration of the neurosurgeon, gynaecologist and the anaesthesiologist [21].

## 2 Pathophysiological and morphological aspects

During pregnancy there are several physiological changes in the mother's body with the primary aim to support the foetus's growth and to enable the normal progression of pregnancy and childbirth. In this adaptive environment of pregnancy a pathological process such as brain tumour can present with very different characteristics and biological behaviour. The background of the

complex pathophysiological and morphological changes in tumours in pregnancy are far from being understood. In the following deep review of the literature, there are two cardinal mechanisms to be considered: endocrine and vascular.

## 2.1 Endocrinological considerations

It has been shown that meningioma growth is enhanced in the progesterone-dominated luteal phase of the menstrual cycle [22]. Following successful conception, within the first four weeks, the estrogen and progesterone secretion becomes limited exclusively to the ovary. In this process the hCG produced by syncytiotrophoblasts is indispensable for maintaining the corpus luteum, therefore hCG plays its key role in the first twenty weeks of pregnancy. However, from week ten onwards the placenta takes over the production of estrogen and progesterone. During pregnancy, the FSH and LH as well as prolactin levels are low due to the negative feedback mechanisms affecting the anterior pituitary. Boyle-Walsh et al. demonstrated, that the glycoproteins FSH, LH and hCG in vitro cell culture inhibit tumour cell proliferation; in contrast, the proteins hPL and PRL stimulate tumour propagation. The changes of plasma concentration of the above mentioned hormones during pregnancy and their effect on meningioma growth are in concert with the notion, that regarding tumour (including meningioma) growth the second and third trimester are crucial and critical [23]. However, the pathognomonic effect of estrogen is questionable. Estrogen receptor (ER) is not expressed in the majority of meningiomas and this phenomenon is not different in the so called 'gestational meningiomas' [20]. It is interesting, that in vitro studies using reverse transcription PCR (RT-PCR) have demonstrated that the ER expression in meningiomas is present in much higher proportion of cases than anticipated based on immunohistochemical results. These contrasting results are probably due to the different sensitivity of the applied techniques; however, the functional activity of receptors remains unknown [24]. The role of progesterone receptor (PR) has been studied in numerous papers. There is inverse relation between protein expression and tumour grade [25]. While the rate of cell division (mitosis) is increasing with higher grade, meningiomas in pregnancy are predominantly low grade (WHO I) with negligible mitotic activity. Hence, it is questionable whether the rapid tumour growth is related to progesterone-induced cell proliferation or not [21-22]. The exact role of progesterone is far from being fully elucidated despite the numerous published research paper on

this topic. Surely, the majority of meningiomas express PR, which can be detected also by immunohistochemistry [26]. The fact that tumour growth is usually occurring in the luteal phase of menstrual cycle or in the second or third trimester of pregnancy, when progesterone plasma concentration is higher, suggests the role of sex hormones in the mechanism [27]. Somewhat contradicting these arguments, PR is expressed not only in meningiomas of females but also in those of males and children; furthermore, the peak of incidence of the tumour is far beyond the fertile age when the serum level of progesterone is relatively low. The moderately increased meningioma risk in women diagnosed with breast cancer is in accordance with the higher risk of breast cancer in females who previously had meningioma, supporting the potential role of hormonal mechanisms in the tumour development [28]. Moreover, long term hormone replacement therapy also raises the possibility of disease, although such correlation has not been shown after use of oral contraceptives [29].

## 2.2 Possible vascular mechanisms

During pregnancy the cardiovascular system shows several significant physiological changes. Stroke volume (which is the volume of blood ejected from the left ventricle per beat) from the 6<sup>th</sup> week of pregnancy till the 28<sup>th</sup> week is increased by 30-40%, and in parallel with these changes the heart rate also accelerates by 15-20/min compared to the non-pregnant period. Plasma volume and red blood cell count increase by 40-50% and by 20-30%, respectively, leading to physiologic haemodilution and decrease of blood viscosity by 20%. Total peripheral resistance is reduced therefore the resting blood pressure should not exceed 140/90 Hg mm. The decreasing albumin production of the liver together with the increasing amount of total body water lead to oedema formation. However, PTBE can be associated with meningiomas independently of pregnancy [11]. Primarily, it accompanies angiomatous and secretory meningioma subtypes [12]. Nassehi examined 43 patients who suffered from meningioma associated with PTBE. His results showed that VEGF protein and mRNA levels correlate with the oedema index (which is calculated from the volume of tumour + PTBE divided by the volume of tumour). Comparing the genders, in women the water content was higher whereas VEGF protein level was lower in the tumour [30]. Another paper suggests that the elevated VEGF protein levels within the oedema are derived from the protein secretion of tumour and not from de novo protein synthesis of PTBE [31]. Consequently, the angiogenic factor produced by the tumour

plays crucial role in PTBE genesis. Furthermore, the risk of recurrence is higher as a consequence of the extension of oedema [2]. As noted, the exact role of VEGF in the growth of gestational meningioma is not clearly understood, also due to the relatively low number of analyzed cases. The body of literature suggesting crucial role of rapid vascular changes in the mechanism is derived mainly from the morphological examination of tumour. Some researchers have identified typical foamy, swollen, oedematous cells in the histopathological meningioma samples resected from pregnant women [32]. Other studies have found that the presence of increased vascularity and focal pathological alterations, such as intra- or extracellular oedema, are significantly higher in the cases of ‘gestational meningioma’, in contrast to meningiomas of non-pregnant women [20]. Although size of the tumour could decrease after child-birth, it could increase again during the next pregnancy; these features suggest a reversible underlying mechanism [18]. Rare benign vascular tumours, such as intracranial capillary haemangioma also mimic meningioma [33]. Consequently, the hemodynamic changes with their reversible nature, probably play a remarkable role in the pathogenesis and growth of the tumour. However, the above mentioned alterations are not detectable in all pregnant women with meningioma. Furthermore, the rapid growth of tumour in pregnancy is not a generally applicable law. Bringing to light the possible role of progesterone in the regulation of brain blood vessel function would facilitate to understand the connection between endocrine mechanisms and vascular changes [34]. More than likely that the endocrine and vascular mechanisms are not acting independently, but rather both responsible for the altered behaviour of ‘gestational meningiomas’ (Table 1).

### 3 Symptoms, diagnostics, therapy

Taking the tumour’s anatomical location into account, there is no general rule regarding clinical symptoms and biological behaviour. Sometimes a small meningioma can cause severe symptoms, whereas a large one can be asymptomatic for a long time. The tumour compresses the surrounding structures leading to complaints and clinical signs. The most frequent symptoms are: headache, dizziness, focal lesions and epileptic fits. Skull base is a common localisation of meningioma, thus its accelerated growth during pregnancy often gives rise to visual disturbances [20]. Extremely large meningiomas cause rapid increase of intracranial pressure. The compression of optic nerve leads to reduced venous return, resulting in a blurry and oedematous papilla on funduscopy. Squeezing of the oculomotor nerve causes functional deficit of intraocular muscles, anisocoria, pupillary dilatation and absence of light reaction. Increased intracranial pressure is also accountable for nausea, vomitus, confusion and finally the patient fall into coma as a consequence of transtentorial herniation and brainstem compression [35]. Because of these unspecific symptoms, differential diagnosis from the other complications of pregnancy could be difficult. The most common conditions showing similar symptoms are: eclampsia, hyperemesis gravidarum and post-partum psychosis [36]. In the process of establishing the accurate diagnosis, the first step is the detailed physical examination. As next, the use of imaging techniques is also essential. During pregnancy, MRI is the preferred choice because X-ray has teratogenic effects. Therapy should be both timely and personalised, depending on the characteristics of intracranial process, stage of pregnancy and general condition of foetus and mother. If possible, the first choice is close observation until labour [37]. Pharmaceutical therapy aims to reduce brain oedema and halt its progression. The wide use of corticosteroids against PTBE is not always effective. Moreover, the long-term side effects of the drug is not negligible. Despite VEGF inhibitors having remarkable pharmaceutical effect, the drugs are contraindicated during pregnancy due to the well-known severe teratogenic side effects (i.e.: phocomelia caused by thalidomide)[38]. Preventing epileptic seizures is a major goal of the therapy, in order to avoid fetal hypoxia during seizures. There should be special emphasis on avoidance and prevention of possible teratogenic effects of any medications and diagnostic procedures. Mannitol administration is not recommended except in cases of life-threatening brain oedema, since it significantly decreases the utero-placental blood flow [39]. Although some reports claim that accurately calculated whole brain radiotherapy

Hormonal (progesterone) effects	Reversible hemodynamical changes
<b>Support the hypothesis</b> <ul style="list-style-type: none"> <li>Female predominance of meningiomas</li> <li>Growth mainly occurs in the 2nd and 3rd trimester, and in the luteal phase of menstruation cycle (when the progesterone plasma level is elevated)</li> </ul>	<b>Support the hypothesis</b> <ul style="list-style-type: none"> <li>Many swollen cells</li> <li>Increased vascularity, intra- or extracellular edema in the tumour</li> <li>Reversibility: regression after childbirth</li> </ul>
<b>Against the hypothesis</b> <ul style="list-style-type: none"> <li>Progesterone receptor expressed in also in meningiomas of males and children</li> <li>The peak incidence is postmenopausal</li> </ul>	<b>Against the hypothesis</b> <ul style="list-style-type: none"> <li>Peritumoral edema occurs in meningiomas of non-pregnant patients</li> <li>These changes are not always detectable in gestational meningiomas</li> </ul>
<b>Unclear</b> <ul style="list-style-type: none"> <li>Link to cell proliferation</li> <li>Role of physiological vascular effects</li> </ul>	<b>Unclear</b> <ul style="list-style-type: none"> <li>Link to hormonal changes</li> </ul>

**Table 1:** The two dominant hypothesis for rapid growth in gestational meningioma

with special emphasis on protecting the abdominal region is a low-risk and effective local therapy during pregnancy [22], focal irradiation of the tumour is currently the preferred option in rapidly growing and malignant meningiomas [40]. Stereotactic radiosurgery (gamma knife) treatment is also often possible, depending on tumour size and localization [41]. Surgical resection is still the main curative treatment of meningiomas, whereby the extent of PTBE is also reduced after a successful neurosurgical intervention. If the tumour is non-resectable, antiprogesterone (i.e. mifepristone) and chemotherapeutic (i.e. hydroxyurea) drugs might be considered. Urgent surgical intervention is usually necessary in cases of malignant meningioma, conventionally untreatable hydrocephalus, and progressively enlarging potentially life-threatening tumours. Brain surgery during pregnancy is extraordinarily risky for both mother and child, thus the continuous intraoperative monitoring as well as the professional high quality cooperation amongst brain surgeons, obstetrician and anaesthesiologist are inevitable [35].

## 4 Conclusion

'Gestational meningioma' is a rare but frequently life-threatening disease that is characterized by unusual behaviour compared to meningiomas of non-pregnant women. The detailed pathophysiology in the background of rapid tumour growth has not been fully understood. Based on available data it is suspected that endocrine and vascular changes play crucial roles. Diagnosis in most cases is possible based on clinical symptoms, physical examination and results obtained by modern imaging techniques. Taking into account the severe and sometimes lethal consequences, often only timely and effective therapy can save the lives of mother and foetus.

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