Litwińczuk Michał, Szydełko Joanna, Szydełko Magdalena. The diagnostic and therapeutic difficulties in management with pheochromocytoma in pregnancy – a review. Journal of Education, Health and Sport. 2019;9(9):543-559. eISSN 2391-8306. DOI http://dx.doi.org/10.5281/zenodo.3442418
http://ojs.ukw.edu.pl/index.php/johs/article/view/7476

The journal has had 5 points in Ministry of Science and Higher Education parametric evaluation. § 8. 2) and § 12. 1. 2) 22.02.2019.

Received: 01.09.2019. Revised: 18.09.2019. Accepted: 18.09.2019.

The diagnostic and therapeutic difficulties in management with pheochromocytoma in pregnancy – a review

Michał Litwińczuk[1a], Joanna Szydełko[1b], Magdalena Szydełko[2c]

[1]Department of Endocrinology, Medical University of Lublin, Poland

[2]Medical Student, I Faculty of Medicine with Dentistry Division, Medical University of Lublin, Poland

[a] mlitwinczuk405@gmail.com, ORCID ID: https://orcid.org/0000-0002-4086-6779

[b] jszydelko@interia.pl, ORCID ID: https://orcid.org/0000-0003-3744-9058

[c] mszydelko@interia.pl, ORCID ID: https://orcid.org/0000-0001-6216-9934

Corresponding author:
Michał Litwińczuk
Department of Endocrinology
Jaczewskiego 8 Street
20-954 Lublin, Poland
phone: +48 81 72 44 668
e-mail: mlitwinczuk405@gmail.com

Abstract

Introduction: Pheochromocytoma (PCC) is a very rare and life-threatening condition in pregnancy. According to different data, it occurs in about 0,00002%-0,007% of pregnant women. The early diagnosis and the proper clinical management play a crucial role in decreasing maternal and fetal mortality.

Aim of the study: This article summarizes the current knowledge about the management with PCC in pregnancy and presents the possible maternal and fetal outcomes.

Description of knowledge: The review revealed, that manifestations of catecholamine-secreting tumors are similar to the most common hypertension-associated problems occurring in pregnancy, such as pre-eclampsia. That is why, timely diagnosis is essential for the mothers and fetuses' survivals. Despite the fact, that the fetus is protected from influence of maternal overproduction of catecholamines due to the presence of placental enzymes activity, there is an enormous risk of spontaneous abortion, fetal growth restriction, premature delivery, when the optimal therapy will not be applied on time. The diagnosis is based on laboratory tests – determination of plasma and urine concentration of catecholamines and imaging tests to localize the tumor, from which only MRI, in 1st and 3rd trimester, and ultrasound examination can be safely used in pregnancy. The guidelines suggest surgical tumor removal as the treatment of choice for women with PCC in pregnancy. The 2nd trimester seems to be the best period for the surgery, however it can be performed only after 10-14 days of effective therapy with α- and β-blockers. The review of literature revealed that, surgical tumor removal carried out before the end of 24. hbd, is safe both for mother and her fetus life.

Conclusions: PCC is a great challenge, because of the extremely rare occurrence in pregnant women and serious complications due to the secretion of catecholamines, which may result in catecholamin crisis, increasing the risk of mortality. Nevertheless, there is still no clear consensus on PCC treatment and further researches are needed to develop the optimal management in this clinical condition.

Key words: pheochromocytoma, pregnancy, maternal complications, fetal complications

Introduction

Pheochromocytomas (PCCs) are rare tumors, which usually develop in adrenal medulla and are composed of chromaffin cells derived from the sympathetic nervous system. They are sometimes genetically determined and may be caused by mutations in 1 of 10 described susceptibility genes. Many different syndromes are associated with the presence of pheochromocytoma, such as familial pheochromocytoma, MEN 2A with mutation in RET proto-oncogene, von Hippel- Lindau- mutation of VHL tumor suppressor gene, neurofibromatosis caused by mutations of NF1 gene on chromosome 17, succinate dehydrogenase (SDH), among which we stand out mutations in SDHA, SDHB, SDHC and SDHD, TMEM 127, MAX-MYC associated factor X [1-3].

The literature overview revealed that the incidence of pheochromocytoma is accounted for approximately 0.95 cases per 1 million patient-years in nearly over 40 years [4]. The frequency of pherochromocytoma occurrence in pregnant women ranges between 0.00002% to 0.007% [1-2,5-9]. The overwhelming majority of pheochromocytomas are benign tumors. According to recent reports, only 10% of these tumors are malignant, of which 10% occur bilaterally and 10% have familial background [3]. That is why, it is important to carry out genetic tests, which allow for making a diagnosis early as well as starting to administer the adequate therapy promptly. Moreover, it seems to be an enormous clinical problem, due to uncommon occurrence, severe symptoms of that disease as well as high mortality, particularly associated with the catecholamine crisis. Therefore, the diagnosis and treatment of pheochromocytoma is a great challenge for clinicians.

The most of PCCs are benign, but one quarter of all tumors are malignant. They statistically occur in nearly 10% of all cases, in which the metastasis generally involved the lymph nodes, liver and lungs. The metastases spreading to the spine seem to be the rarity. So far, only 17 cases of metastatic pheochromocytoma to the spine have been reported in the literature. However, purely one author described probably the first case of metastatic

pheochromocytoma to the spine in pregnant woman [10]. It is worth to emphasize that the fetus is not exposed to maternal overproduction of catecholamines due to the placental catechol-O-methyltransferase and monoamine oxidase activity, which break down these hormones [2]. Despite this, the complications in fetus may occur after the development of disturbances at the placental interface, so the essential issue is to preserve adequate uteroplacental circulation [5]. The changes in maternal blood pressure strongly affect the uteroplacental circulation, because of the lack of its own autoregulation. High concentrations of catecholamines may induce profound vasoconstriction of the maternal uterine arterial circulation and uteroplacental insufficiency as a result. Considering above-mentioned data, there is an enormous risk of hypoxia of the fetus, spontaneous abortion, fetal growth restriction or premature delivery. The implementation of adequate therapy is greatly important to reduce incidence of possibly life-threatening situations for the mother and the fetus. According to *Ghalandarpoor-Attar SN. et al.*, early diagnosis and treatment can decrease maternal and fetal mortality and morbidity as well as severe complications from around 50% to 5% and 15% respectively [1,3,9].

Aim of the study

The aim of this review was to present the diagnostic and therapeutic difficulties in management with pheochromocytoma in pregnancy. Moreover, we also discussed possible maternal and fetal complications that may occur at early gestational age, in advanced pregnancy, and during or after delivery. Additionally, we tried to assess an ideal moment for optimal decision of pregnancy termination in women with pheochromocytoma.

Materials and methods

The available articles published between January 2015 and August 2019 were subjectively selected due to its usefulness in showing the difficulties in the diagnostic process of pheochromocytoma in pregnant women. Moreover, data which reveals maternal and fetal outcomes was shown as well. Publications in English and Polish in the EBSCO and the PubMed database have been analyzed using key words: pheochromocytoma, pregnancy, maternal complications, fetal complications.

Pheochromocytoma in pregnancy – fetal and maternal complications

Pheochromocytoma diagnosed during pregnancy constitutes a great challenge for clinicians of different specialties, such as endocrinologists, gynecologists, neonatologists, and surgeons as well as it requires the interdisciplinary approach. Maternal and fetal

complications may occur at early gestational age, in advanced gestation, and during or after delivery.

Based on analyzed data, due to multidisciplinary intensive care, in most of cases any complications in newborn were observed as well as the status of women was without significant negative outcomes. It is also worth to underline that the cesarean section was usually the method of choice as the form of delivery in above-mentioned cases [3,8, 21, 24, 25, 28-30, 34].

In scientific articles available in the Pubmed database one of the papers analyzed 15 pregnant women with hypertension, of whom ten were diagnosed with pheochromocytoma, three with primary aldosteronism and two with Cushing's syndrome [11]. All women had severe high blood pressure diagnosed in pregnancy before conception. In every single case, increased risk for pregnant women and their babies, high risk of stillbirth and operative delivery were reported [11]. Both maternal and fetal complications were summarized in Table 1 [3, 8, 18, 21, 24, 27, 29, 30, 35].

Binderup ML. et al. presented 30 individuals women after delivery with von Hippel-Lindau syndrome to assess the impact of pregnancy on the course of the disease and stated that pregnancy was not stimulated VHL tumors development [33]. Moreover, it was noted, that intensive supervision over pregnant women with VHL mutations is not necessary due to a naturally slower tumor development in women from fertile ages group [33].

The difficulties in differential diagnosis of incidentaloma during pregnancy

Clinical manifestations of pheochromocytomas in pregnant women are less severe than in general population and are manifested by headache, palpitations, as well as sweating and paroxysmal hypertension at a young age, which especially occur before 20 weeks of pregnancy. It can be caused by the secretion of catecholamines, therefore early diagnostic tests should be performed [8]. Considering, that above-mentioned symptoms might appear in 90% of pregnant women before delivery [5], which are similar to others clinical conditions such as preeclampsia, gestational hypertension, diabetes mellitus as well as aldosteronoma, making a diagnosis of pheochromocytoma is a particular challenge in clinical practice.

It should be underline that, the high blood pressure episodes, which are characteristic for preeclampsia, significantly rarely occur before 20th week of pregnancy [6] and what is more important, this condition is more often associated with proteinuria and raised uric acid

concentration [5]. Additionally, catecholamine-induced cardiomyopathy, which differs from pheochromocytoma and preeclampsia should be taken into consideration [2].

Moreover, it should be strongly remembered in the differential diagnosis, that pheochromocytoma occurs in genetically determined syndromes, such as MEN 2, both 2A-Sipple's and 2B-Williams-Pollock subtypes, Gorlin-Vickers, Wagenmann-Froboese syndrome, von Hippel-Lindau and type 1 neurofibromatosis, paraganglioma-pheochromocytoma (PPGL) syndrome [15-16]. According to the latest data, there are only 29 case reports of pregnant women with MEN 2A syndrome. It seems to be a special diagnostic problem, because it predisposes to the development of medullary thyroid cancer in 90-100% of individuals, pheochromocytomas in 50% and hyperthyroidism in 15-25% of cases, therefore it requires early measuring of parathyroid hormone serum level and ultrasound examination of the neck [14].

Another clinical entity, that should be taken into consideration in differential diagnosis is PPGL syndrome, which is also very rare condition and can be similar to preeclampsia or gestational hypertension [17]. Catecholamine-secreting tumors can be divided into intra-adrenal tumor, known as pheochromocytomas and extra-adrenal paragangliomas. Sympathetic or parasympathetic ganglia constitute the area, where tumors can develop. Among them sympathetic paragangliomas are catecholamine-secreting tumors and are mainly located in the abdomen or thorax. Moreover, they can mimic a severe preeclampsia [17]. The literature overview of 77 cases of pregnancies with catecholamin-secreting tumors performed between 2000-2011, revealed that 80% of individuals were diagnosed with pheochromocytomas and 20% with paragangliomas [17].

Another cause of hypertension in pregnancy is primary hyperaldosteronism (PHA) with the prevalence of about 0,6%-0,8% cases in pregnant women [16]. PHA may result in severe hypertension, preeclampsia, preterm delivery and fetal loss [16]. Diagnostic tests include the measurement of aldosterone and renin levels as well as plasma renin activity (PRA), which are significantly higher than in primary hypoaldosteronism in non-pregnant women or in the general population. A PRA levels ranging from 1 and 4 ng/ml/h are usually associated with hypokalemia and hypertension and suggest PHA [16].

The standard laboratory diagnostic tests for pheochromocytomas include 24-hour urine collection to detect the level of fractionated catecholamines in plasma: metanephrine, nor-metanephrine and 3-methoxytyramine [10,12,13,14,15]. What is more, the ranges for

catecholamines in pregnant women do not differ as compared to general population. Also an auxiliary parameter may be the level of chromogranin A, which is collected as co-secreted substance with catecholamines, and can act as a prohormone that stimulates the rise of active peptides [14].

Furthermore, radiological techniques, which are as important as laboratory tests, should be discussed. The recommended imaging diagnostic of pheochromocytoma during pregnancy is based on abdominal ultrasound examination and non-contrast MRI (sensitivity 98%-100%, specificity 70%) [12,14-15]. According to our knowledge, the best time to perform the MRI examination is first and third trimester of pregnancy [15]. Iodine-123 metaiodobenzylguanidine (MIBG) scintigraphy, which is performed in the general population, is contraindicated in pregnancy due to exposure to ionizing radiation and potential fetal injuries as consequences [10].

Table 1. Characteristics of pheochromocytoma in pregnant women - analysis the series of case reports from PubMed datebase between 2015-2019.

Case study (Reference)	Female age [Years]	Gestational age at the diagnosis [Weeks]	Number of following pregnancy	Symptoms during diagnosis	Side of tumor's localization in adrenal glands	Diameter of the tumor [mm]	Hormonal status	Pharmacological treatment	Surgical treatment	Maternal complications	Fetal complications
Santos DRet al., 2015 [3]	24	33	first	hypertension, preeclampsia	left	5,2 x 4 cm (in CT made after delivery) 5,6 x 4,9 cm (in MRI of abdominal)	Urine noradrenaline was elevated and plasma renin activity was about 10 times higher than normal levels. Plasma renin activity: 55.9 ng/ml/h (reference value: 1.9-6 ng/ml/h), urine noradrenaline 339 mcg/24hs (reference value: <97 mcg/24hs), serum noradrenaline 4,102.6 pg/ml (reference value: 114-352 pg/ml)	She was started on i.v. hydralazine 10 mg and magnesium sulfate 40 mEq, and was later given p.o. methyldopa 2g/day and nifedipine retard 40 mg/day . The patient was transferred to the ICU with a hypertensive emergency and acute pulmonary edema controlled with i.v. sodium nitroprusside; she was also given p.o.l hydrochlorothiazide 25 mg/day, captopril 100 mg/day, and amlodipine besylate 5 mg/day. 13 days after discharge the patient was hospitalized with a hypertensive crisis and acute diffuse abdominal pain.	cesarean section	hypertensive crisis	The fetus was in distress due to centralization of the blood flow. The baby weight was 1,389 grams, APGAR scores was 4 and 8; the baby died 14 days later
Shah S et.al, 2017 [8]	26	35	first	hypertension	right	61 x 58 x 49 mm	Two separate plasma metanephrine samples revealed: isolated elevated nor-metanephrine greater than 9999 pmol/L (normal5900 pmol/L), normal metanephrine (5500 pmol/L). Urinary fractionated meta-nephrines revealed elevated noradrenaline of 11,610 nmol/day (5780 nmol/day) with normal adrenaline excretion (530nmol/day)	Methyldopa 250mg twice a day at 25. hbd, and this was titrated to 500mg three times a day. Labetalol 100 mg daily at 33. hbd. was added. Alpha blockademedication was started in conjunction with labetalol 200mg twice daily. Due to the lack of availability of phenoxybenzamine, prazosin 0.5 mg twice daily was commenced and titrated up to 3.5 mg thrice daily On 9th day of admission, phenoxybenzamine 30 mg twice daily was substituted for prazosin	after cesarean section at 38. hbd	without any complications	initial management included a temporary admission to the neonatal intensive care unit for 1 h of continuous positive airway pressure for respiratory distress and blood pressure monitoring
Orioli L,et al. 2016 [29]	27	24	first	asymptomatic, clinical observation due to MEN2A syndrome-C634R ret mutation	right	40 × 35 mm	24-houruринary collection was immediately requested but performed only at 24. hbd, showing very high concentrations of metanephrines (2519 g/24 h, normal values 0–320g/24h) and normeta-nephrines (3120 g/24 h, 0–390 g/24 h) consistent with the diagnosis of pheo-chromocytoma	α-blockers Propranolol	laparoscopic adrenalectomy after cesarean section at 38. hbd	without any complications	without any complications

							At 25. hbd 3- to 10-fold elevated urinary concentrations of catecholamines and metabolites				
Weingarten M et.al, 2015 [30]	24	Late third trymester	first	hypertension	bilateral	14 mm x 18 mm	significantly raised metadrenalin at a level of 1849 mcg/24 h (normal level 80–510 mcg/24 h) with normal nonmetadrenalin levels was noted	Phenoxibenzamine, proporanolol	bilateral adrenalectomy 5 months after cesarean section	severe hypertension	without any complications
E Paula FA et al.,2018 [20]	32	22	first	hypertension, sporadic episodes of headaches, sweating, face flushing symptoms of headaches, facial flushing, and sweating started at 17 weeks of gestation	right	101 × 95 mm	Metanephrine 6873.2 µg/24 h (reference value <280 µg/24 hours) Normetanephrine 6299.2 µg/24 hours (reference value <732 µg/24 hours) on 24 hours urine collection	Methyldopa, α- and β-blockers	laparoscopic adrenalectomy at 24. hbd	directly after operation without any complications	directly after tumor resection without any complications 5 weeks after she underwent emergency cesarean section The newborn, who was born alive, died prematurely within 48 hours.
Malinowski AK et al., 2015 [34]	30	23 6/7	first	vomiting, chest pain, severe hypertension	not known	not known	not known	Prazosin, Phenoxibenzamine, β-blockers	urgent cesarean section	without any complications	post-procedure fetal bradycardia
Kishu Kitayama et al.,2015 [18]	32	12	first	no symptoms	bilateral	right: 49×44x42 mm; left: 73×61x75 mm	elevated meta-nephrine (14 mg/24h; normal, 0.005–0.20 mg/24h) and normeta-nephrine levels (12 mg/24 h; normal, 0.10–0.28/24 h) in 24-h urine sample	Doxazosine- α-blockers	no data	without any complications	without any complications
Kiroplastis K et al., 2015 [35]	34	9	first	episods of hypertension, palpitation, headaches, sweating	right	90 x 75 mm	24 h-urine VMA28.0 [1.8–6.7 mg/24 h] 24catecholamines 889[14–108 μg/24 h]	Terazosin- α-blockers, Atenolol- β-blockers	no data	without any complications	without any complications
Łubińska M et al., 2018 [27]	30	12	first	anxiety, palpitations, recurring headaches, hypertension, tachykardia,	left	80 × 62 × 68 mm	markedly elevated excretion of normetanephrine (5760 µg/24 h; reference range, 162–527 µg/24 h) 3 -methoxytyramine (1817µg/24h; reference range, 103–434 µg/24 h) in urine collection	metoprolol, nitrendipine, and methyldopa before diagnosis. After doxazosin and labetalol. Presurgical treatment consisted of doxazosin (32 mg/d), metoprolol (3 × 50 mg/d), and nitrendipine (2 × 60 mg/d).	no data	without any complications	without any complications

Langton K et al., 2018 [24]	36	34	first	hypertensive crisis, insulin-dependent gestational diabetes, sweating	left	2,4 cm diameter	Increased plasma concetrations and urinary outputs of normetanephrine and normal values for metanephrine	Prior to pregnancy At 34. hbd treatment was intensified using methyldopa, nifedipine, dihydralazin and urapidil	surgical removal of the tumor after cesarean section	severe labile blood pressure, hyperglycemia and blurred vison	without any complications
Özveren B et al., 2019 [21]	36	15	first	no symptoms	right	11 x 7,5 cm	Increased catecholamine and urinary plasma concentrations	Did not receive any medical treatment. During surgery blood preassure was stabilized with phentolamine and esmolol	laparotomy at 17. hbd, cesarean section, delivery of healthy twins at term	without any complications	without any complications
Naghshine E et al., 2016 [25]	27	2 days after cesarean section	first	headache, confusion, nausea, vomiting, shortness of breath, tachypnea, hypertension	left	58 mm x 50 mm×30 mm in abdominal CT	Epinephrine = 65.2 (NL: 1.7–22.4 μg/24 h), norepinephrine = 364 (NL: 12.5–85.5 μg/24 h), metanephrine = 2071 (NL: 30–180 mcg/24 h), normetanephrine = 1337 (NL: 103–390 mcg/24 h), and VMA = 17.18 (NL: 1.4–6.5 mg/24 h) were increased in 24 h urine collection	Phenoxybenzamine and propranolol	cesarean section at term pregnancy due to fetal distress adrenalectomy	hypertension crisis, tachycardia	without any complications
Donatini G et al., 2018 [28]	No data	between the 10th and the 29th weeks of pregnancy	ten patients	six patients had none to mild symptoms, while four had complications of paroxysmal hypertension	no data	no data	Urinary metanephrine collection.	All patients were treated either with α/β blockers or calcium channel blockers	7 patients: laparo-scopic adrenal-ectomy before delivery 3 out of these 7 patients had a bilateral PHEO - adrenalectomy of the larger tumor during pregnancy, followed by a planned C-section and a subsequent contra-lateral adrenal-ectomy within a few months after deli-very. 3 patients had emergency surgery for maternal or fetal complications, with C-section followed by concomitant or delayed adrenal-ectomy.	no data	all newborns from the group of planned surgery were healthy, while 2 out 3 newborns within the emergency surgery group died shortly after delivery secondary to cardiac and pulmonary complications
Radfar MH et al., 2018 [31]	27	20th weeks of pregnancy	first	severe intermittent headache, hypertension crisis	left	3,1 × 3,3 cm in abdominal ultrasound examination	Elevated 24-hour urinary excretion of metanephrines and normetanephrines	α-adrenergic blockade with phenoxybenzamine was performed	laparoscopic tumor removal at 19. hbd	without any complications	without any complications
Melvin A et	34	16th weeks of	first	postural	paragangliom	whole-body	Elevated 24-hour urinary	α- and β-adrenergic blockade	cesarean section at	no data	without any

al., 2015[32]		pregnancy		dizziness, hypertension	a	MRI examination revealed a retroperitoneal mass-paraganglioma	excretion of metanephrines and normetanephrines	was used	36. hbd		complications
Alvarado M et al., 2016 [38]	38	not known	not known	not known	not known	not known	not known	α- and β-adrenergic blockade was used	surgical removal	without any complications	without any complications

Treatment of pheochromocytoma during pregnancy

There is still no clarify consensus, which may provide fully defined therapeutic procedures helpful to apply the optimal medical treatment of pheochromocytoma in pregnant women [15-16,18-19]. In numerous reported cases, α-blockers were the drugs of choice to counteract the effects of catecholamines secretion [15-16,18-20]. It is important to use the right dose of α-blockers, because they may lead to uteroplacental vasoconstriction [20]. Phenoxybenzamine and doxazosin are most commonly used to control blood pressure, however the advantage of applying doxazosin is more selective potential of α1-adrenoreceptor blockade than in case of phenoxibenzamine, which in turn seems to be method of choice of pre-operative management with catecholamine excess [22]. Furthermore, non-selective α-blockers might cross the placenta barrier and in some cases they are able to cause neonatal hypotension and respiratory depression, and that is why life functions should be strongly monitored [19-21]. Phenoxybenzamine administration may also provide to reflex tachycardia at a mother, which is rarely observed than in case of the doxazosin administration. However, both of these drugs can caused increased heart rate and β-blockers are also used to counteract this effect [22].

Another drug, which is used to treatment hypertension-associated with PCC is methyldopa. Nevertheless, it is not preferred because of the worsen blood pressure control [2]. The use of methyldopa should be terminated due to the possibility of interference with the measurements of urine metanephrine concentration [2].

The special clinical condition, which requires the intensive care is the catecholamine crisis and the situation when the drug cannot be administered orally. The best solution is the administration of phentolamine or labetalol intravenously.

The treatment of choice is surgical removal of the tumor in second trimester, performed only after starting the use of α-blockers, which should be carried out for 10 to 14 days before surgery [16, 36, 38]. *Reitman E. et al*. presented the case of the female patient, who was admitted to the hospital in pregnancy with paroxysmal palpitations, denying the occurrence of hypertension. However, the therapy with phenoxybenzamine was started to prevent the possibility of hypertension crisis occurring during delivery. The phenylephrine was used in place of phenoxybenzamine due to its responsiveness during surgery [23]. Nevertheless, the therapeutic effect was not achieved and vasopressin was added [23].

The laparoscopic adrenalectomy is recommended, when the diameter of tumor mass amounts below 7 cm and gestational age is earlier than 24. hbd [15,25]. However, this surgical procedure is connected with carbon dioxide insufflation, which may lead to hemodynamic complications [12]. The open surgical removal should be performed simultaneously with the termination of pregnancy by cesarean section, which is the preferred method of delivery [15,25]. Vaginal delivery is associated with higher mortality rate (31%) as compared with cesarean section (19%) [25].

Early diagnose and management have been attributed to improvement in maternal outcomes. The prompt diagnosis and adequate clinical management, has decreased the maternal mortality from 48% to 2% as the reported cases noted [25]. Moreover, it was accompanied with better fetal outcomes and if the appropriate management was performed, the pregnancy loss was estimated only in about 11% of all pregnant women. That is why, further studies are indispensable to investigate the novel, safety and precise at the same time diagnostic strategy to identify the pheochromocytoma during the antenatal period, which should be helpful to reduce maternal mortality and fetal loss due to timely implementation of appropriate therapy.

Conclusions

Pheochromocytoma is a great diagnostic and therapeutic challenge, due to the extremely rare occurrence, especially in pregnant women and serious complications occur due to the secretion of catecholamines by the tumor. It may result in catecholamine crisis, which increases the risk of mortality. The 24h urinary catecholamine collection or raised plasma catecholamines as well as MRI in 1st and 3rd trimester or ultrasound examination to localize the tumor are crucial to make an appropriate diagnosis. PCC should be differentiated with pre-eclampsia, so it needs to be suspect in women with hypertension, in absence of proteinuria, odedema or persistent glucosuria. To date, there is no clear consensus on pheochromocytoma treatment and an interdisciplinary approach is indispensable. However, according to the guidelines, the treatment of choice is surgery. It should be carried out before the end of 24 weeks of pregnancy, if it would be safely done for the mother and her fetus. Nevertheless, further research is needed to develop optimal management in this clinical condition during pregnancy.

References:

1. van der Weerd K, van Noord C, Loeve M, Knapen MFCM, Visser W, de Herder WW, et al. ENDOCRINOLOGY IN PREGNANCY: Pheochromocytoma in pregnancy: case series and review of literature. Eur J Endocrinol. 2017;177(2):R49-R58. doi: 10.1530/EJE-16-0920.
2. Prete A, Paragliola RM, Salvatori R, Corsello SM. Managment of catecholamin-secreting tumors in pregnancy: A REVIEW. Endocr Pract. 2016;22(3):357-70. doi: 10.4158/EP151009.RA.
3. Santos DR, Barbisan CC, Marcellini C, dos Santos RM. Pheochromocytoma and pregnancy: A case report and review. [Article in English, Portuguese] J Bras Nefrol. 2015;37(4):496-500. doi: 10.5935/0101-2800.20150078.
4. Januszewicz W, Prejbisz A, Januszewicz A, Pęczkowska M. Pheochromocytoma — Disease that Can Stimulate Many Different Syndromes. Nadciśn Tętn. 2002;6(3):217–227.
5. Iijima S. Impact of maternal pheochromocytoma on the fetus and neonate. Gynecol Endocrinol. 2019;35(4):280-286. doi: 10.1080/09513590.2018.1540568.
6. Giampaolino P, Della Corte L, Formisano C, Cuomo L, Maurea S, Romeo V, et.al Successful management of a third-trimester pregnancy complicated by pheochromocytoma: case report. Gynecol Endocrinol. 2018;34(12):1016-1018. doi: 10.1080/09513590.2018.1480712.
7. Kaluarachchi VTS, Bulugahapitiya U, Arambewela M, Gunathilake S.Successful Management of Pheochromocytoma Detected in Pregnancy by Interval Adrenalectomy in a VHL Patient.Case Rep Endocrinol. 2018;2018:9014585. doi: 10.1155/2018/9014585.
8. Shah S, Edwards L, Robinson A, Crosthwaite A, Houlihan C, Paizis K.A rare cause of hypertension in pregnancy: Phaeochromocytoma.Obstet Med. 2017;10(2):83-84. doi: 10.1177/1753495X16669995.
9. E Paula FA, Dos Santos RI Junior, Ferruzzi OA, Melo RO, Takaku M. Laparoscopic approach to pheochromocytoma in pregnancy: case report. Int Braz J Urol. 2018;44(3):629-633. doi: 10.1590/S1677-5538.
10. Liu S, Song A, Zhou X, Kong X, Li WA, Wang Y, et al. Malignant pheochromocytoma with multiple vertebral metastases causing acute incomplete paralysis during pregnancy: Literature review with one case report.Medicine (Baltimore). 2017;96(44):e8535. doi: 10.1097/MD.0000000000008535.

11. Quartermaine G, Lambert K, Rees K, Seed PT, Dhanjal MK, Knight M, et al. Hormone-secreting adrenal tumours cause severe hypertension and high rates of poor pregnancy outcome; a UK Obstetric Surveillance System study with case control comparisons. BJOG. 2018;125(6):719-727. doi: 10.1111/1471-0528.14918.

12. Lenders JWM, Langton K, Langenhuijsen JF, Eisenhofer G. Pheochromocytoma and Pregnancy. Endocrinol Metab Clin North Am. 2019;48(3):605-617. doi: 10.1016/j.ecl.2019.05.006.

13. Remón-Ruiz P, Aliaga-Verdugo A, Guerrero-Vázquez R. Pheochromocytoma in neurofibromatosis type 1 during pregnancy. Gynecol Endocrinol. 2017;33(2):93-95. doi: 10.1080/09513590.2016.1254181.

14. Tingi E, Kyriacou A, Verghese L. Recurrence of phaeochromocytoma in pregnancy in a patient with multiple endocrine neoplasia 2A: a case report and review of literature. Gynecol Endocrinol. 2016;32(11):875-880. doi: 10.1080/09513590.2016.1236242.

15. Eschler DC, Kogekar N, Pessah-Pollack R. Management of adrenal tumors in pregnancy. Endocrinol Metab Clin North Am. 2015;44(2):381-397. doi: 10.1016/j.ecl.2015.02.006.

16. Malha L, August P. Secondary Hypertension in Pregnancy. Curr Hypertens Rep. 2015;17(7):53. doi: 10.1007/s11906-015-0563-z.

17. Kim HJ, Yang SH, Yang SH, Han SS, Kim GJ. Extra-adrenal paraganglioma masquerading as severe preeclampsia. Obstet Gynecol Sci. 2018;61(4):520-523. doi: 10.5468/ogs.2018.61.4.520.

18. Kitayama K, Kashiwagi S, Amano R, Noda S, Ohira G, Yamazoe S, et al. A case of bilateral pheochromocytoma during pregnancy. BMC Surg. 2015;15:55. doi: 10.1186/s12893-015-0041-1.

19. Ghalandarpoor-Attar SN, Ghalandarpoor-Attar SM, Borna S, Ghotbizadeh F. A rare presentation of pheochromocytoma in pregnancy: a case report. J Med Case Rep. 2018 9;12(1):37. doi: 10.1186/s13256-017-1549-z.

20. E Paula FA, Dos Santos RI Junior, Ferruzzi OA, Melo RO, Takaku M. Laparoscopic approach to pheochromocytoma in pregnancy: case report. Int Braz J Urol. 2018;44(3):629-633. doi: 10.1590/S1677-5538.

21. Özveren B, Ulugöl H, Türkeri L. Normotensive, Oversized Pheochromocytoma in Twin-Pregnancy: Analysis of Therapeutic Challenges in a Rare Case. Case Rep Urol. 2019;2019:7141060. doi: 10.1155/2019/7141060.

22. Alvarado M, Ramirez-Vick M, Allende-Vigo M, Mendez-Latalladi W, Agosto M, Gonzalez R, et al. Pheochromocytoma in pregnancy: A case Report. Bol Asoc Med P R. 2016;108(1):95-98.

23. Reitman E, Monteleone M, Smiley RM. Phenylephrine infusion test to evaluate alpha blockade in a pregnant patient with pheochromocytoma.Int J Obstet Anesth. 2016;25:90-91. doi: 10.1016/j.ijoa.2015.08.005

24. Langton K, Gruber M, Masjkur J, Steenblock C, Peitzsch M, Meinel J, et al. Hypertensive crisis in pregnancy due to a metamorphosing pheochromocytoma with postdelivery Cushing's syndrome. Gynecol Endocrinol. 2018;34(1):20-24. doi: 10.1080/09513590.2017.1379497.

25. Naghshineh E, Shahraki AD, Sheikhalian S, Hashemi L.Pheochromocytoma after Cesarean Section.Int J Prev Med. 2016;7:60. doi: 10.4103/2008-7802.178534.

26. Mita K, Tsugita K, Yasuda Y, Matsuki Y, Obata Y, Matsuki Y, et.al.A successfully treated case of cardiac arrest after Caesarean section complicated by pheochromocytoma crisis and amniotic fluid embolism.J Anesth. 2017;31(1):140-143. doi: 10.1007/s00540-016-2281-3.

27. Łubińska M, Hoffmann M, Jendrzejewski J, Kobiela P, Kobiela J, Sworczak K.Successful surgical treatment of pheochromocytoma during pregnancy.Pol Arch Intern Med. 2018;128(5):322-323. doi: 10.20452/pamw.4247.

28. Donatini G, Kraimps JL, Caillard C, Mirallie E, Pierre F, De Calan L, et al.Correction to: Pheochromocytoma diagnosed during pregnancy: lessons learned from a series of ten patients.Surg Endosc. 2018;32(9):3901. doi: 10.1007/s00464-018-6145-9.

29. Orioli L, Debièvе F, Donckier J, Mourad M, Lois F, Maiter D. Pheochromocytoma during pregnancy: Case report and review of recent literature. Ann Endocrinol (Paris). 2017;78(5):480-484. doi: 10.1016/j.ando.2017.05.004.

30. Weingarten M, Rao S, Lincoln K. Successful management of phaeochromocytoma in the third trimester of pregnancy with the use of rapid sequential alpha-adrenergic blockage. Eur J Obstet Gynecol Reprod Biol. 2016;198:174-175. doi: 10.1016/j.ejogrb.2015.12.025.

31. Radfar MH, Shakiba B, Afyouni A, Hoshyar H. Laparoscopic management of paraganglioma in a pregnant woman: a case report. Int Braz J Urol. 2018;44(5):1032-1035. doi: 10.1590/S1677-5538.

32. Melvin A, Kinsley B. Hypertension presenting early in pregnancy. Clin Case Rep. 2015;3(12):1056-1057. doi: 10.1002/ccr3.392.

33. Binderup ML, Budtz-Jørgensen E, Bisgaard ML. New von Hippel-Lindau manifestations develop at the same or decreased rates in pregnancy. Neurology. 2015;85(17):1500-1503. doi: 10.1212/WNL.0000000000002064.

34. Malinowski AK, Maxwell C, Sermer M, Rubin B, Gandhi S, Silversides CK. Pheochromocytoma in a Pregnant Woman With Prior Traumatic Aortic Injury. Obstet Gynecol. 2015;126(5):1089-1094. doi: 10.1097/AOG.0000000000000909.

35. Kiroplastis K, Kambaroudis A, Andronikou A, Reklou A, Kokkonis D, Petras P, et al. Dealing with Pheochromocytoma during the First Trimester of Pregnancy. Case Rep Obstet Gynecol. 2015;2015:439127. doi: 10.1155/2015/439127.

36. Maharaj R, Parbhu S, Ramcharan W, Baijoo S, Greaves W, Harnanan D, et al. Giant Cystic Pheochromocytoma with Low Risk of Malignancy: A Case Report and Literature Review. Case Rep Oncol Med. 2017;2017:4638608. doi: 10.1155/2017/4638608.

37. Warner KI, Poole-Ward RL, Martinez A, Jones K, Burgis JT, Smith RS. Postpartum transabdominal laparoscopic adrenalectomy for pheochromocytoma presenting with abruption and hypertensive emergency. Am Surg. 2015;81(1):E34-35.- Brak dostępu

38. Alvarado M, Ramirez-Vick M, Allende-Vigo M, Mendez-Latalladi W, Agosto M, Gonzalez R, et al. Pheochromocytoma in pregnancy: A case Report. Bol Asoc Med P R. 2016;108(1):95-98.