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Multiple myeloma during pregnancy as a challenge in clinical practice – a review

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Abstract

Introduction:

Multiple myeloma (MM) is a hematological malignancy characterized by an abnormal proliferation and accumulation of monoclonal plasma cells. MM typically affects the elderly

people with the median age at the diagnosis between 65 to 74 years. Only in < 2% of cases it is observed <40 years, that is why its incidence in gestation is extraordinary.

Aim of the study:

The aim of this study was to present the review of the literature concerning the cases of MM in pregnancy as a great challenge in clinical practice. Moreover, the most common symptoms, diagnostic as well as therapeutic strategies of MM in pregnancy were discussed. The influence of the status of the newborns and the pregnant women were also analyzed.

Description of knowledge:

Our overview revealed 44 cases of MM in pregnancy. It was predominantly diagnosed in the 2nd or 3rd trimester and the median age of women was 34 years. The caesarean section seemed to be the recommended method of delivery and the mean gestational age at the delivery was 35. hbd. Nearly all of the newborns were born premature, but healthy. The symptoms were similar to those in the general population (bone pain, signs of anemia, hypercalcemia) and in single cases the renal failure, hypertensive or bilateral breast lumps were observed. Steroids were predominantly administered and the therapy based on cyclophosphamide, urethane or interferon was the rarity.

Conclusions:

MM in pregnancy seems not be a contraindication for maintaining of gestation. The management may be problematic due to the lack of guidelines concerning the methods of treatment as well as its safety for the fetus. Based on the literature, steroids are the most certain and efficient anti-MM drugs in pregnancy. However, the majority of newborns are premature, which is also associated with the possibility of later complications.

Introduction

Malignant neoplasms during pregnancy contribute to various diagnostic, therapeutic and social challenges and require the interdisciplinary approach. Management in that clinical condition is frequently associated with the necessity of the prompt implementation of therapy, however the different aspects, such as gestational age, stage of the disease, potential effects on the fetus or patient's decision should be strongly taken into consideration. According to the latest data, cancers occurring in pregnancy is diagnosed in approximately 1:1000 pregnant women with still increasing incidence, mainly due to the rising median age at pregnancy [1]. The solid tumors, such as cervical cancer, breast cancer and malignant melanoma constitute the most

common malignancies during pregnancy. Hematologic malignancies associated with pregnancy are even uncommon, which leads to the fact that the randomized controlled trials and the long-term follow-up are limited [2]. Among all of the hematologic malignancies Hodgkin and high-grade non-Hodgkin lymphomas (1:1000 – 1:6000) as well as acute leukemias (1:75 000 – 1: 100 000) are encountered predominantly during gestation [1,3]. Multiple myeloma (MM) is considered to be a malignancy typically affecting the elderly people with the median age at the diagnosis ranging between 65 to 74 years [4]. Based on the epidemiological data, only in < 2% of cases MM is observed under 40 years, and what is worth noting - MM slightly common involved men than women, especially in black population, that is why its incidence in pregnant women is extraordinary [5,6]. The first case of MM complicating pregnancy was reported in 1965 by Giordano C. [7]. Based on our knowledge, only 43 cases of MM during gestation and 1 case with light chain deposition disease associated with MM have been presented until 2019 [3-35].

Multiple myeloma is a multi-stage hematological malignancy characterized by an abnormal proliferation and accumulation of monoclonal plasma cells producing monoclonal immunoglobulin or its fragments [9]. The most common prodromal symptoms of that disease in general population are fatigue, weight loss and bone pain (70% of cases). Moreover, the signs of anemia (70%), hypercalcemia (25%) as well as neurological disorders, recurrent infections or renal failure are usually noted in the course of MM [5,10]. Considering above-mentioned manifestations, making the diagnosis of MM during gestation might be doubtful, because some of that signs are strongly associated with the natural course of pregnancy.

In most cases the diagnosis was made in the second or third trimester and the severity of the disease has been determined using the Durie & Salmon classification as well as in some cases by International Staging System (ISS) [5,11]. The criteria of that scales was presented in Table 1. and Table 2.

The therapy strategies of MM in pregnancy are not clarify due to the rarity of this condition and the lack of randomized trials evaluating the safety and efficiency of chemiotherapy (CTH) applied in general population. Moreover, there are ambiguous scientific reports in literature about the use of CTH in pregnancy. So far, in the described cases of MM complicating pregnancies, the treatment schemes with steroids (prednisolone, dexamethasone), co-administration of melphalane, cyclophosphamide, vincristine and prednisone have been most commonly used, and there are isolated cases of the treatment based on cyclophosphamide or interferon [11,12]. Taken into consideration the fact, that in nearly all of pregnant women, the

bone lesions in the course of MM were observed, the cesarean section was the most common method form of the delivery [9].

Table 1. Durie & Salmon classification

Parameter	Stage I	Stage II	Stage III
	All of the criteria below	**One or more of the criteria below**	**One or more of the criteria below**
Hemoglobin	**>10 g/dl**	**8.5 - 10.0 g/dl**	**<8.5 g/l**
Calcium	**<3.0 mmol/l**	**3.0 mmol/l**	**>3.0 mmol/l**
M-Protein			
IgA	**<30 g/l**	**30 – 50 g/l**	**>50 g/l**
IgG	**<50 g/l**	**50 – 70 g/l**	**>70 g/l**
Urin light chain	**<4 g/24h**	**4-12 g/24h**	**>12 g/24h**
Bone X-ray	**normal bone structure**	**minor bone lesions**	**advanced bone lesion**
Subclassification	**Stage A**	**Serum creatinine < 177 μmol/l**	
	Stage B	**Serum creatinine ≥ 177 μmol/l**	

Table 2. International Staging System Score (ISS)

Stage	**Criteria**	**Median survival (months)**
I	**Serum β_2-microglobulin < 3.5 mg/l and albumin ≥ 3.5 g/100 ml**	**62**
II	**Neither stage I nor III**	**44**
III	**Serum β_2-microglobulin ≥ 5.5 mg/l**	**29**

Aim of the study

The aim of this study was to present the review of the literature concerning the rare cases of multiple myeloma during pregnancy as a great challenge in clinical practice. Furthermore, the most common symptoms, diagnostic procedures as well as therapy strategies of MM in pregnant women were discussed. The influence of the status of the newborns and the pregnant women were also analyzed.

Materials and methods

The available literature in English was subjectively selected due to its usefulness in showing clinical approach to the most common symptoms, diagnosis pathways and therapy of MM in pregnant women. Moreover, literature which reveals inconsistency in results was shown as

well. Articles in the EBSCO and the PubMed database have been analyzed using keywords: multiple myeloma, pregnancy, symptoms, diagnosis, therapy strategies.

Description of knowledge

Hematological malignancies occurring in pregnant women constitutes the great challenge for clinicians of various specialties. The main question, which should be taken into consideration should be related to the strategies for this extremely rare condition and the appropriate as well as safe for both woman and the fetus time for implementation of therapy, so if we have to apply the rule: 'watch and wait' or 'act immediately'. Multiple myeloma is a malignancy typically affecting the elderly people, so its occurrence in gestation seems to be a rarity and based on our knowledge, only 43 cases of MM and 1 case of light chain deposition disease associated with MM were described. Our literature overview revealed that the age of pregnant women with MM ranged from 21-43 years with the peak of incidence at 34 years. What is more, the MM was generally diagnosed during second (16 cases) or third trimester (11 cases) and the others in the first trimester (10), in postpartum period (3) and before pregnancy (2). All cases of MM during pregnancy, considering women age and gestational age at the diagnosis, most common symptoms, Durie & Salmon classification, ISS, gestational age at the delivery, the status of newborns, time of treatment implementation as well as anti-MM therapy in pregnancy and MM – therapy after delivery, since 1965 to 2019 were summarized in Table 3.

Table 3. Multiple myeloma and pregnancy – review of case reports (1965 – 2019).

Case number	Age at diagnosis	Gestational age at the diagnosis	Symptoms	Durie & Salmon	ISS	Gestational age at delivery	Status of newborn	Time of treatment implementation	Anti-MM therapy in pregnancy	MM - therapy	References
1	40 years	second trimester	bone pain	III	not known	38. hbd	healthy	during pregnancy, 1st trimester	cyclophospha-mide	not known	*Giordano C., 1965 [7]*
2	35 years	first trimester	bone pain	not known	not known	38. hbd	not known	during pregnancy	urethane, radiotherapy	urethane, radiotherapy	*Kosova LA, 1966 [26]*
3	42 years	first trimester	bone pain, headache	not known	not known	38. hbd	healthy	during pregnancy	urethane	not known	*Rosner F,1968 [27]*
4	38 years	third trimester	severe anemia, jaundice	not known	not known	35. hbd	healthy	not	not	not	*Talerman A, 1971 [28], 1987 [29]*
5	21 years	second trimester	bone pain	not known	not known	39. hbd	healthy	during pregnancy	cyclophospha-mide	cyclophosphamide	*Lergier JE, 1974 [24]*
6	29 years	postpartum	anemia, hypercalcemia, lethargy	II	not known	not known	healthy	after	not	not known	*Harster GA, 1987 [30]*
7	30 years	postpartum	bone pain	not known	not known	not known	healthy	after	not	not known	
8	32 years	third trimester	anemia, bone pain	not known	not known	36. hbd	healthy	after	not	radiotherapy, chemiotherapy	*Malee MP, 1990 [31]*
9	33 years	second trimester	anemia	II B	not known	36. hbd	healthy	after	not	not known	*Caudle MR, 1990 [32]*
10	27 years	second trimester	severe refractory anemia	III A	not known	39. hbd	healthy	after	not	not known	*Pajor A, 1991 [33]*
11	41 years	first trimester	anemia, bone pain	III B	not known	38. hbd	not known	during pregnancy	interferon	not known	*Sakata H, 1995 [25]*
12	34 years	first trimester	proteinuria, bone lesions, anemia	II A	I	34. hbd	healthy	after	not	thalidomide, dexamethasone + tandem auto-allo SCT)	*Maglione A, 2003 [34]*

13	41 years	second trimester	bone pain, anemia, renal failure	III B	not known	34. hbd	healthy	during pregnancy	dexamethasone	dexamethasone, high-dose melphalane + ASCT	*Forthman CL, 2004 [17]*
14	34 years	first trimester (15. hbd)	excessive vomiting, light headedness, lethargy, hypercalcemia, anemia, bone lesions	III B	not known	19. hbd	abortion	after	not	velcade, adriamycin, high dose dexamethasone	*Malik S, 2006 [35]*
15	32 years	postpartum	increased lethargy, reduced apetite, nausea, vomiting, weight loss, back pain, two lumps on the forehead, renal failure	III B	not known	------	healthy	after	not	high-dose dexamethasone, the CTH with vincristine, adriamycin, dexamethasone was planned	*Lee JC, 2007 [19]*
16	32 years	third trimester (31. hbd)	severe back pain, pathologic fractures of vertebrae, anemia	III A	II	32. hbd	healthy	during pregnancy (3rd trimester)	dexamethasone	vincristine, doxorubicin, dexamethasone	*Zun KH, 2008 [15]*
17	39 years	third trimester (32. hbd)	back pain, bilateral lower limb weakness spinal cord compression, urinary retention	III A	I	32. hbd	healthy	during pregnancy (3rd trimester)	idarubicin, dexamethasone	etoposide, cisplatin, cytrabine, methylprednisolone	*Quinn J, 2009 [13]*
18	42 years	third trimester (28. hbd)	anemia, proteinuria, hypertension	III	I	35. hbd	healthy (low birth weight)	after	not	not known	*Dabrowska DM, 2010, [20]*
19	33 years	second trimester (14. hbd.)	anemia, thrombocytopenia, morning sickness, pain in the right hip	plasma cell myeloma		33. hbd	healthy	during pregnancy (2nd trimester)	dexamethasone	thalidomide, cyclophosphamide, dexamethasone	*Wilmott F, 2010 [36]*
20	31 years	second trimester (18. hbd)	asthenia, hyperemesis, anemia bone pain	III	not known	18. hbd	abortion	after	not	vincristine, adryamycin and dexamethasone, followed by interferon	*Rodríguez LGR, 2010 [37]*
21	32 years	first trimester	bone pain	not known	not known	36. hbd	healthy	during pregnancy	cyclophosphamide, melphalane, vincristine, prednisone + melphalane, prednisone		*Avilés A, 2011 [9]*
22	37 years	second trimester	bone pain	not known	not known	38. hbd	healthy	during pregnancy	cyclophosphamide, melphalane, vincristine, prednisone, doxorubicine + melphalane, prednisone		

23	24 years	first trimester	bone pain	not known	not known	33. hbd	healthy	during pregnancy	cyclophosphamide, melphalane, vincristine, prednisone, interferon + melphalane, prednisone		
24	35 years	first trimester	bone pain	not known	not known	34. hbd	healthy	during pregnancy	dexamethasone, all trans-retinoic acid and interferon + melphalane, prednisone		
25	39 years	second trimester	bone pain	not known	not known	38. hbd	healthy	during pregnancy	dexamethasone, all trans-retinoic acid and interferon		
26	32 years	third trimester	bone pain	not known	not known	39. hbd	healthy	during pregnancy	cyclophosphamide, melphalane, vincristine, prednisone		
27	34 years	second trimester (24. hbd)	lower back pain, anemia, proteinuria	III A	I	32. hbd	healthy	during pregnancy (2^{nd} trimester)	prednisolone	bortezomib, cyclophosphamide, dexamethasone	*Kasenda B, 2011 [3]*
28	33 years	first trimester (12. hbd)	asymptomatic proteinuria, progression to symptomatic MM at 31. hbd	I A	not known	34. hbd	healthy	after	not	bortezomib, dexamethasone	*Borja de Mozota D, 2011 [5]*
29	39 years	second trimester (26. hbd)	bilateral breast lumps	III A	II	34. hbd	healthy	during pregnancy (3^{rd} trimester)	dexamethasone	thalidomide, dexamethsone	*Bouzguenda R, 2013 [21]*
30	38 years	before, relapse at third trimester (28. hbd)	low back pain, anemia	II A	not known	37. hbd	healthy	after	not	cyclophosphamide, bortezomib, dexamethasone + ASCT and high-dose melphalane	*Brisou G, 2013 [11]*
31	34 years	second trimester (24. hbd)	anemia, nearly asymptomatic	III A	I	35. hbd	healthy (low birth weight)	during pregnancy, 3^{rd} trimester	dexamethasone	bortezomib and dexamethasone + ASCT and high-dose melphalane	*Smith D, 2014 [14]*
32	38 years	third trimester (32. hbd)	back pain, leg weakness, decreased sensation, difficulty voiding urine	III A	I	32. hbd	healthy	after	not	radiotherapy, cyclophosphamide, idarubicin, dexamethasone + etoposide, methylprednisolonecytarabine, cisplatin + ASCT	

33	33 years	second trimester (14. hbd)	hypercalcemia, right hip pain	III A	I	33. hbd	healthy	during pregnancy, 3rd trimester	dexamethasone	radiotherapy, cyclophosphamide, thalidomide and dexamethasone, followed by high-dose melphalan and ASCT	
34	30 years	not known	hemorrhage after a spontaneous abortion, relapsed during second pregnancy	III A	I	not known	abortion, second pregnancy - healthy	after	not	vincristine, doxorubicin and dexamethasone + ASCT with high dose melphalane	*Khot AS, 2014 [16]*
35	32 years	second trimester (14. hbd)	compression fractures of spine	III A	I	14. hbd.	abortion	after	not	vincristine, doxorubicin and dexamethasone + radiotherapy	
36	35 years	not known	not evaluated	III A	I	not known	not known	after	not	lenalidomide, dexamethasone	
37	22 years	third trimester (32. hbd)	nausea, vomiting, rib and back pain, hypertension, anemia, thrombocytopenia, acute renal insufficiency, hypercalcemia laboratory parameters indicative of pancreatitis	III B	not known	32. hbd	healthy	after	not	not known	*McIntosh J, 2014 [18]*
38	37 years	second trimester (27. hbd)	anemia	III A	II	34. hbd	healthy	after	not	bortezomib, lenalomide, dexamethasone	*Cabañas-Perianes V, 2016 [12]*
39	43 years	third trimester (28. hbd)	pathological rib fractures, pulmonary infection, anemia, hypercalcemia, renal failure	III B	III	30. hbd	healthy	during pregnancy, 3rd trimester	high-dose methylprednisolone	bortezomib, dexamethasone	*Jurczyszyn A, 2016 [4]*

40	39 years	third trimester (31. hbd)	back pain, anemia, hypercalcemia	III A	I	36. hbd	healthy	during pregnancy, 3rd trimester	dexamethasone	bortezomib, dexamethasone	
41	34 years	before pregnancy	mild cytopenias	I A	I	on time	healthy	after	not	not evaluated	
42	not known	first trimester	not evaluated	I A	II	not known	healthy	after	not	not evaluated	
43	not known	during pregnancy	not evaluated	III A	I	not known	healthy	after	not	not evaluated	
44	34 years	second trimester (20. hbd)	abdominal distention, extremity lower limb edema	LCDD associated with MM		24. hbd	still-born	after	not	bortezomib, thalidomide, dexamethasone	*Kim MJ, 2018 [8]*

The most common symptoms of MM during pregnancy

Initially, the clinical manifestation of MM in pregnancy is often not straightly linked to that hematological malignancy due to the fact that some of the signs might occur in uncomplicated pregnancies. The most common symptoms detected by women are strongly similar to those in patient with MM from general population. Bone pain was observed in approximately 64% of all cases as a consequence of osteolytic and pathological changes in bone and usually was located in lumbar spine, pelvis, ribs or long bones [5]. However, MM during pregnancy was also manifested by life-threatening and requiring urgent surgical intervention situation of spinal cord compression, which occured as severe back pain, urinary retention as well as bilateral lower limb weakness [13-16]. The mild lesions in bones structure sometimes led to pathological fractures of them [17].

The other most common manifestations were the anemia ranging from mild to severe (45%) as well as hypercalcemia (14%) and vomiting, lethargy as a consequence [5,18]. Furthermore, *McIntosh J et al.* reported a case of MM in pregnant women associated with preeclampsia, pancreatitis, nephrolithiasis likely secondary to high-grade hypercalcemia (20 mg/dl) [18]. Based on symptoms presented by patient, in the first line, bone fat necrosis secondary to acute pancreatitis, metastatic cancer (primary source uncertain), multiple myeloma, Paget disease (osteodystrophia deformans), primary lymphoma of the bone, leukemia as well as rhabdomyosarcoma were taken into consideration.

The MM may initially manifests as a renal failure only in 30% in general population, but it is rather extraordinary in pregnancy [4,17,19]. So far, there is only one case, which described the developed acute renal failure (creatinine: 3190 μmol/l, urea 49.0 mmol/l) requiring replacement therapy. Moreover, the hypertension [18,20] extremity lower limb edema [8] or threatening hemorrhage after spontaneus miscarriage [16] were noted as the prodromal symptoms of MM during gestation. It is worth to emphasize, that *Bouzguenda R. et al.* described the remarkable manifestation of MM in the form of bilateral breast lumps with atypical clinical and radiological features [21]. What is more, these solid masses rapidly increased their sizes (13.9 x 11.5 cm in the left breast and 6.5 x 5.5 cm in the right breast). The ultrasound examination revealed, that this is the hypoechoic heterogenous mass with posterior acoustic shadowing and macrolobulation, and the biopsy indicated the presence of atypical plasmacytoid cells with eccentric nucleus suggestive of plasma cell neoplasm infiltrating mammary glands. Considering the fact that soft tissues are usually occupied later in the course of MM, as well as the not clear radiological features, ejection a suspicion of MM was difficult, because other,

more common causes such as benign or malignant breast tumors was taken into consideration in this condition at first.

Diagnostic strategies

Making the diagnosis of MM during pregnancy is a great challenge, because some of laboratory abnormalities (such as lower hemoglobin level, proteinuria) do not arouse suspicion of obstetrician due to physiological changes in maternal body. That is why, in most cases the diagnosis was made after excluding other common causes. The spectrum of laboratory tests predominantly included peripheral blood morphology, marking the concentration of calcium, β_2-microglobulin, determination of light chains in blood and urine as well as the blood indicators of renal function (creatinine, urea, uric acid) [9].

Moreover, the bone marrow smears examination to revealed the presence of increased percentage (> 10%) of monoclonal plasmocytes was performed. Based on these tests, the disease advancement was defined by the Durie & Salmon classification in 68% pregnant women. However, the cytogenetic evaluation were conducted occasionally and usually using the fluorescence in situ hybridization (FISH) method.

The other challenge in clinical practice provides the occurrence of bone lesions in pregnant women during MM and the difficulties in making a choice of appropriate imaging test. It is commonly known that the X-rays, computed tomography (CT) as well as positron-emission tomography – CT scans are contraindicated in gestation period due to their potential harmful effect on the fetus [22]. The first trimester of pregnancy (mainly > 2. hbd and < 15 hbd.) is the special time when the dose becomes crucial important factor due to organogenesis processes and the potential teratogenic properties of radiation. The American College of Radiology underline that the dose of radiation cannot exceed 50 mGy during all trimesters of pregnancy [23]. However, the chest X-ray with a special protective cover on the abdominal and pelvis area as well as the radiographs on the adequate body areas with the strong suspicion of the fractures (based on symptoms reported by the patient, eg. from head, arms, legs) are acceptable [4]. Magnetic resonance imaging (MRI) should be the method of choice in the pregnant women, nevertheless, we should remember that the gadolinium-based contrast agents may penetrate though placenta to the fetus [22]. Moreover, it worth to emphasize, that the MRI is useful rather for detection the bone morrow invasion during MM than for providing information about the osteoporosis, so the utility of whole-body MRI in this clinical condition should be discussed.

Cabañas-Perianes V. et al. underlined the important value of serial and systematical assessment of pregnant woman condition based on physical examination and laboratory analysis weekly or

every 2 weeks as well as fetal ultrasound examination, which should help clinicians to avoid later complications [12].

The current approach to the anti - MM therapy in pregnancy – what do we know?

The choice of the appropriate time of therapy implementation during pregnancy complicated by MM requires the knowledge about adverse effects of the drugs on the fetus and its development. The safety of regimens used during pregnancy was classified by the Food and Drug Administration (FDA) agency and it was presented in Table 4 [4].

Table 4. The Food and Drug Administration's classification of drugs used in pregnancy

Category	**A**	**B**	**C**	**D**	**X**
Description	well-controlled human studies indicate no fetal risk	animal studies indicate fetal risk not confirmed by human studies or animal studies do not indicate fetal risk and well-controlled human studies are unavailable	well-controlled human studies are lacking and animal studies are unavailable or indicate adverse effects to the fetus	human studies or investigational or postmarketing data indicate fetal risk; benefits may be acceptable despite potential risks	animal/human studies or investigational or postmarketing data indicate fetal risk that clearly outweighs any possible benefit
Drugs	-	**glucocorticoids**	**cyclophosphamide, interferon**	**bortezomib, vincristine, melphalane**	**thalidomide, lenalidomide, pomalidomide**

According to the analyzed cases, twenty three from 40 pregnant women did not received any anti-MM drugs during pregnancy. It is worth to underline, that in above-mentioned cases only not specific to that hematological malignancy therapy was applied in order to compensate the abnormalities associated with MM, such as anemia or hypercalcemia [5,16-18,21,23,25-27,30-34]. The anti-MM treatment was administered in 17 cases. Steroids, especially dexamethasone (8 women) or high-dose (methyl)prednisolone (2 pregnant) were used preferably. *Kasenda B., et al*. proposed to assume the steroids e.g. prednisolone 25-100 mg every second day as the first line strategy to achieve the stabilization of disease before partum (especially > 34. hbd) [3]. In the described case report, the 57% decrease in the blood concentration of κ light chains and normalization of parameters of the red cell system were achieved by administered of 50 mg prednisone every second day.

Furthermore, the combination of conventional multi-drug CTH was used in six patients during pregnancy [9]. The CTH schemes contain cyclophosphamide, melphalane, vincristine, prednisone and what is worth noting, no adverse effect in the patients' children were documented during 19 years follow-up. There are also two cases in the available data, where

the clinicians decided to apply the cyclophosphamide as the leading therapy before partum [5,7,24]. The patient received cyclophosphamide at the total dose of 800 mg in the first case and 50 mg/day until delivery in the second one. There were no obstetric complications during gestation and the intrauterine growth of the fetus was proper in both cases as well as the newborns were born without any complications. *Kasenda B., et al*. suggested cyclophosphamide as the second choice anti-MM treatment during pregnancy [3].

Furthermore, interferon in one case and urethane alone or in combination with radiotherapy was used during pregnancy without any noticeable alterations for the fetus [25-27]. The induction to the therapy the novel agents, such as bortezomib (proteasome inhibitor) or lenalidomide are contraindicated in pregnancy due to its potential teratogenic effects and the FDA classified this drugs to the category X and, what should be remembered, the contraception is required 4 weeks before and after as well as in all period of therapy using these regimens [4].

The effect of this hematologic malignancy on the status of newborns and pregnant women

The literature overview revealed that the median gestational age at the delivery was 35. hbd (30. – 39. hbd), nevertheless three pregnancies were terminated at 14., 19. and 18. hbd. due to the severe bone lesions or spinal cord compression [16,35,37]. Moreover, seven cases of preterm induced deliveries (> 32. hbd) due to the presence of severe bone lesions, were reported. The most common form of delivery was caesarean section (60% of cases). Only ten gestation was terminatation by vaginal deliveries and no complications were observed [5,7,19,25-27,29,30-31,33].

What is more, nearly 23 newborns (72%) were premature, but generally healthy. So far, two cases of newborns with the low birth weight (LBW) were noted [14,20] and one with the Apgar score 5 at birth [18]. Considering above data, the status of newborns comes from pregnancies complicated by MM do not vary from those with non-MM pregnancy.

Besides, there is no consensus in the literature about the probable effect of pregnancy on the course of this hematological malignancy. *Borja de Mozota D. et al*. concluded that the pregnancy seems no to have an influence on MM [5]. Nevertheless, it should be underlined that the gestation is the time when the immunological changes take place [38]. The most crucial issue is probably the shifts in the TH1/TH2 balance toward a majority of Th2 group. *Lee JC. et al*. reported a case of female initially diagnosed with monoclonal gammopathy of undetermined significance (MGUS), which rapidly progressed to multiple myeloma three months after pregnancy [19]. The author observed, that the level of intereleukin-6 (IL-6) as well as insulin-like growth factor 1 (IGF-1), which are commonly known as factors involving in the growth of

the MM cells, are increased during pregnancy. Moreover, the changes in hormones concentration may lead to the progression of the disease. However, the further studies are needed to clarify this issue.

The most important problem is concerned about the fertility of women after MM treatment. It is commonly known, that the intensive chemotherapy schemes may result in the retaining of fertility, especially when the total body irradiation is administered. Nevertheless, there are limited cases of pregnant women with MM, when the stem cell transplant in pregnancy was performed as a part of therapy and the child was born without any negative changes [16]. In that conditions, the high doses of alkylating agents, such as cyclophosphamide are recommended.

Conlusions

The occurring of multiple myeloma during pregnancy seems not to be a contraindication for maintaining the gestation. However, it is indispensable to noted that the management in this condition may be problematic due to the lack of guidelines concerning the methods of treatment as well as its safety for the fetus. Moreover, the caesarean section seems to be the method of choice of delivery in pregnant women because of the probably presence of the lesions in the spinal cord or pelvic bones. Nevertheless, the most of newborns are premature, which is also associated with the possibility of developing later complications. According to the literature overview, steroids, especially dexamethasone, are the most safe and efficient anti-MM drug administered during pregnancy.

References

1. Mahmoud HK, Samra MA, Fathy GM. Hematologic malignancies during pregnancy: A review. J Adv Res. 2016; 7(4):589-596. doi: 10.1016/j.jare.2016.02.001.

2. Lavi N, Horowitz NA, Brenner B. An update on the management of hematologic malignancies in pregnancy. Womens Health (Lond). 2014; 10(3):255-2566. doi: 10.2217/whe.14.17.

3. Kasenda B, Rückert A, Farthmann J, Schilling G, Schnerch D, Prömpeler H, et al. Management of multiple myeloma in pregnancy: strategies for a rare challenge. Clin Lymphoma Myeloma Leuk. 2011; 11(2):190-197. doi: 10.1016/j.clml.2011.03.009.

4. Jurczyszyn A, Olszewska-Szopa M, Vesole AS, Vesole DH, Siegel DS, Richardson PG, et al. Multiple Myeloma in Pregnancy--A Review of the Literature and a Case Series. Clin Lymphoma Myeloma Leuk. 2016;16(3):e39-45. doi: 10.1016/j.clml.2015.11.020.

5. Borja de Mozota D, Kadhel P, Dermeche S, Multigner L, Janky E. Multiple myeloma and pregnancy: a case report and literature review. Arch Gynecol Obstet. 2011; 284(4):945-950. doi: 10.1007/s00404-011-1985-8.

6. Kumar SK, Callander NS, Alsina M, Atanackovic D, Biermann JS, Chandler JC, et al. Multiple Myeloma, Version 3.2017, NCCN Clinical Practice Guidelines in Oncology. J Natl Compr Canc Netw. 2017; 15(2):230-269.

7. Giordano C. [Multiple myeloma and pregnancy. (1st case in the world literature)]. Matern Infanc (Sao Paulo). 1965; 24(2):158-184.

8. Kim MJ, Kim JH, Kim IY, Lee SB, Park IS, Han MY, et al. Light Chain Deposition Disease Associated With Multiple Myeloma Developing in Late Pregnancy. Iran J Kidney Dis. 2018; 12(2):132-134.

9. Avilés A, Neri N. Multiple myeloma and pregnancy. Am J Hematol. 2011; 86(1):81-82. doi: 10.1002/ajh.21876.

10. Rajkumar SV. Multiple myeloma. Curr Probl Cancer. 2009; 33(1):7-64. doi: 10.1016/j.currproblcancer.2009.01.001.

11. Brisou G, Bouafia-Sauvy F, Karlin L, Lebras L, Salles G, Coiffier B, et al. Pregnancy and multiple myeloma are not antinomic. Leuk Lymphoma. 2013; 54(12):2738-2741. doi: 10.3109/10428194.2013.786069.

12. Cabañas-Perianes V, Macizo M, Salido E, Blanquer M, Araico F, Melero-Amor A, et al. 'Management multiple myeloma during pregnancy: a case report and review'. Hematol Oncol. 2016; 34(2):108-114. doi: 10.1002/hon.2184.

13. Quinn J, Rabin N, Rodriguez-Justo M, Choi D, Yong K. Multiple myeloma presenting with spinal cord compression during pregnancy. Ann Hematol. 2009; 88(2):181-182. doi: 10.1007/s00277-008-0558-9.

14. Smith D, Stevens J, Quinn J, Cavenagh J, Ingram W, Yong K. Myeloma presenting during pregnancy. Hematol Oncol. 2014; 32(1):52-55. doi: 10.1002/hon.2088.

15. Zun KH, Choi HM. Multiple myeloma presenting as vertebral compression during pregnancy. Int J Gynaecol Obstet. 2008; 100(1):89-90. doi: 10.1016/j.ijgo.2007.05.041.

16. Khot AS, Prince HM, Harrison SJ, Seymour JF. Myeloma and pregnancy: strange bedfellows? Leuk Lymphoma. 2014; 55(4):966-968. doi: 10.3109/10428194.2013.837163.

17. Forthman CL, Ponce BA, Mankin HJ. Multiple myeloma with a pathologic fracture during pregnancy. A case report. J Bone Joint Surg Am. 2004; 86(6):1284-1288. doi: 10.2106/00004623-200406000-00024.

18. McIntosh J, Lauer J, Gunatilake R, Knudtson E. Multiple myeloma presenting as hypercalcemic pancreatitis during pregnancy. Obstet Gynecol. 2014; 124(2 Pt 2 Suppl 1):461-463. doi: 10.1097/AOG.0000000000000361.

19. Lee JC, Francis RS, Smith S, Lee R, Bingham C. Renal failure complicating myeloma in pregnancy. Nephrol Dial Transplant. 2007; 22(12):3652-3655. doi: 10.1093/ndt/gfm277.

20. Dabrowska DM, Gore C, Griffiths S, Mudzingwa M, Varaday S. Anaesthetic management of a pregnant patient with multiple myeloma. Int J Obstet Anesth. 2010; 19(3):336-339. doi: 10.1016/j.ijoa.2010.03.010.

21. Bouzguenda R, Khanfir A, Toumi N, Chaaben K, Hentati Y, Ayadi L, et al. Multiple myeloma presenting as bilateral breast lumps in pregnant woman. Int J Hematol. 2013; 98(4):487-490. doi: 10.1007/s12185-013-1420-y.

22. American College of Obstetricians and Gynecologists' Committee on Obstetric Practice. Committee Opinion No. 656: Guidelines for Diagnostic Imaging During Pregnancy and Lactation. Obstet Gynecol. 2016; 127(2):e75-80. doi: 10.1097/AOG.0000000000001316.

23. ACR practice guideline for imaging pregnant or potentially pregnant adolescents and women with ionizing radiation. 2008.

24. Lergier JE, Jiménez E, Maldonado N, Veray F. Normal pregnancy in multiple myeloma treated with cyclophosphamide. Cancer. 1974; 34(4):1018-1022. doi: 10.1002/1097-0142(197410)34:4<1018::aid-cncr2820340409>3.0.co;2-4.

25. Sakata H, Karamitsos J, Kundaria B, DiSaia PJ. Case report of interferon alfa therapy for multiple myeloma during pregnancy. Am J Obstet Gynecol. 1995; 172(1 Pt 1):217-219. doi: 10.1016/0002-9378(95)90120-5.

26. Kosova LA, Schwartz SO. Multiple myeloma and normal pregnancy. Report of a case. Blood. 1966; 28(1):102-111.

27. Rosner F, Soong BC, Krim M, Miller SP. Normal pregnancy in a patient with multiple myeloma. Obstet Gynecol. 1968; 31(6):811-820.

28. Talerman A, Serjeant GR, Milner PF. Normal pregnancy in a patient with multiple myeloma and sickle cell anaemia. West Indian Med J. 1971; 20(2):97-100.

29. Talerman A. Successful pregnancy in patients with multiple myeloma. Arch Pathol Lab Med. 1987; 111(10):895-896.

30. Harster GA, Krause JR. Multiple myeloma in two young postpartum women. Arch Pathol Lab Med. 1987; 111(1):38-42.

31. Malee MP. Multiple myeloma in pregnancy: a case report. Obstet Gynecol. 1990; 75(3 Pt 2):513-515.

32. Caudle MR, Dodd S, Solomon A. Multiple myeloma in pregnancy: a case report. Obstet Gynecol. 1990; 75(3 Pt 2):516-518.

33. Pajor A, Kelemen E, Mohos Z, Hambach J, Váradi G. Multiple myeloma in pregnancy. Int J Gynaecol Obstet. 1991; 35(4):341-342. doi: 10.1016/0020-7292(91)90669-v.

34. Maglione A, Di Giorgio G, Petruzzelli F, Longo MP. Multiple myeloma diagnosed during early pregnancy: a case report. Eur J Obstet Gynecol Reprod Biol. 2003; 111(2):214-215. doi: 10.1016/s0301-2115(03)00217-3.

35. Malik S, Oliver R, Odejinmi F. A rare association with hyperemesis: pregnancy and multiple myeloma. J Obstet Gynaecol. 2006; 26(7):693-695. doi: 10.1080/01443610600929961.

36. Wilmott F, Agarwal N, Heath M, Stevens J, Chakravatti S. Plasma cell myeloma diagnosed in pregnancy. BMJ Case Rep 2010, 2010. doi: 10.1136/bcr.04.2010.2901

37. Rodríguez LGR, Lianes OA, Padrón CH, Martínez EE. The multiple myeloma and the pregnancy: First case report in Cuba. Rev Cuba Hematol Immunol Hemoter 2010; 26:70-75.

38. Reinhard G, Noll A, Schlebusch H, Mallmann P, Ruecker AV. Shifts in the TH1/TH2 balance during human pregnancy correlate with apoptotic changes. Biochem Biophys Res Commun. 1998; 245(3):933-938. doi: 10.1006/bbrc.1998.8549.