Diagnosis and management of multiple myeloma during pregnancy: case report, review of the literature, and an update on current treatments

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***Abstract*:** The simultaneous occurrence of pregnancy and multiple myeloma (MM) is rare. The challenge of diagnosing MM during pregnancy is demonstrated in the case presented here. Despite the rarity of concurrent MM and pregnancy, this possibility should be considered in patients with signs and symptoms that may be attributed to MM so as not to delay the diagnosis and decision about pregnancy continuation and initiation of an appropriate and safe therapy to the mother and fetus. Treating physicians should be aware of the potential effects of MM therapies on the fetus and pregnancy outcomes.

Keywords: pregnancy, multiple myeloma, diagnosis, therapy

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Introduction

Multiple myeloma (MM) is a neoplastic proliferation of plasma cells in the bone marrow, accounting for 1% of all cancers and approximately 10% of all hematological malignancies.[1] The median age at MM diagnosis is 67–70 years and only 3% of the patients are diagnosed before 40 years of age.[2] Moreover, MM is approximately 1.5 times more prevalent in men compared with women.[3] Therefore, the simultaneous occurrence of pregnancy and MM is rare. The first case describing MM diagnosis during a pregnancy was published in 1965.[4] Between 1965 and 2020, 44 cases of MM, diagnosed around or during pregnancy, were reported in the literature.[2,4–33] The most common early symptoms of MM are bone pain (58% of patients), fatigue (32%), and recurrent infections.[34,35] End-target organ damage according to the CRAB criteria includes hypercalcemia (28%), renal failure (48%), anemia (73%), and lytic bone lesions (20–25%).[35] Some of these symptoms may also be attributed to the normal course of pregnancy. The challenge of diagnosing MM during pregnancy is demonstrated in the case presented here. The patient had signs that were primarily ascribed to her pregnancy and therefore the investigation was initially directed toward pregnancy-related disorders, such as iron deficiency, preeclampsia, or primary kidney disorder. The patient provided written consent for publishing this case report. The case report followed the CARE guidelines.[36]

Case report

A 40-year-old previously healthy woman, gravida 12, para 10, was admitted for an investigation due to elevated blood pressure (180/115 mmHg) and acute renal failure (serum creatinine 1.5 mg/dL, previously normal) at gestational week 16 of index pregnancy. The patient was asymptomatic. Although she had a history of gestational hypertension during her three most recent pregnancies, she was not followed and was never treated for it. Notable laboratory findings included normocytic anemia, hemoglobin 9.4 g/dL, platelets 272 K/μL, and white blood cells 7.69 K/μL. There was no evidence of iron deficiency (iron 70 μg/dL, transferrin 277 mg/dL, ferritin 151.2 mg/mL). Serum albumin, lactate dehydrogenase, and

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electrolytes were within normal range. Total urine protein collected over 24 h was 1.3 g.

Therapy with labetalol 200 mg was started, and the patient was followed at the pregnancy high-risk unit in collaboration with the nephrology unit. During this period, blood pressure remained high and stable and renal function deteriorated to 2.06 mg/dL during week 22.

A kidney core needle biopsy, performed at week 23 + 4, showed 25 normocellular glomeruli without signs of active glomerular disease. No evidence of glomerular capillary wall thickening was observed. The interstitium showed focally prominent infiltration by leukocytes with multiple eosinophils and lymphocytes. Masson trichrome stain highlighted about 20% fibrosis. The tubules demonstrated multiple areas of tubulitis while the vessels showed no significant changes.

The morphological picture was compatible with tubulointerstitial disease with a prominent acute inflammatory component.

Immunostaining for cytomegalovirus, herpes simplex virus, and polyomavirus was negative. Congo red staining was negative for amyloid material. Immunofluorescence staining for IgA, IgG, IgM, C3, C4, C1q, kappa, lambda, fibrinogen, and albumin deposits was also negative. Scanning electron microscopy showed two normocellular glomeruli with prominent thinning of the glomerular basement membrane, and tubules with signs of epithelial cell damage.

The ultrastructural findings were consistent with thin membrane disease associated with tubular damage.

At 25 weeks of pregnancy, serum electrophoresis and immunofixation showed an unquantifiable IgG kappa monoclonal band. Serum IgG was 582 mg/dL (normal 700–1600), IgA 43 mg/dL (normal 70–500), and IgM 22 mg/dL (normal 40–280). Serum free light chain assay demonstrated high levels of kappa light chain 3120 mg/L (normal 3.3–19.4), preserved lambda 7.3 mg/L (normal 5.7–26.3), and a significantly skewed κ/λ ratio of 427.7 (0.26–1.65). Repeated 24-h urine protein collection demonstrated 2.21 g of urine protein, of which 1.91 g were Bence Jones protein. Bone marrow (BM) biopsy revealed infiltration by 70–80% kappa light chain-restricted plasma cells. Congo red stain was negative for amyloid. Fluorescent *in situ* hybridization (FISH) testing of plasma cells showed del13q and *t*(11;14). Whole-body magnetic resonance imaging (MRI) revealed lack of homogeneity along the spine vertebrae with multiple 'salt and pepper' foci. Focal lesions, 8 mm in diameter, were observed in the D8 vertebra and in the left pedicle of the D3 vertebra. Focal lesions, 17 mm in diameter, were observed in the left ilium wing and several bilateral tiny lesions were noted in the iliac bones. The BM along the thighs was inhomogeneous with no evidence for focal lesions (Figure 1).

The findings obtained from the MRI scan, BM biopsy, and the monoclonal proteins observed in the blood and urine all led to the diagnosis of oligosecretory IgG kappa MM, Revised International Staging System (R-ISS) 2, with predominantly kappa light chain secretory disease.

Upon the diagnosis of active MM with anemia, renal and skeletal injuries, there was a clear indication for treatment initiation. Considering that the patient did not wish to terminate the pregnancy, together with the advanced gestational age, therapy with high-dose dexamethasone (HDD) 40 mg/d was initiated.

HDD was administered on days 1–4, 9–12, and 17–20. After one treatment cycle there was no response: serum-free kappa remained stable at 2760 mg/L and serum creatinine was unchanged. Therefore, weekly cyclophosphamide (CTX) 500 mg/m^2 was added to HDD on gestational week 27, resulting in partial response with a reduction in serum-free kappa to as low as 1540 mg/L. Creatinine improved to 1.21 mg/dL. The patient signed an informed consent for this treatment.

Therapy was continued during gestational weeks 27–34 with no further reductions in serum-free kappa light chain and in serum creatinine. Fetal development continued uneventfully, and fetal growth was appropriate for its gestational age.

On gestational week 35, increased creatinine level (1.27 mg/dL) and blood pressure (140/90 mmHg) were observed.

Due to the bony lesions in the pelvis observed by MRI, which increased the concern for a vaginal delivery, an elective caesarian section was performed on gestational week 36. A healthy female

baby, weighing 1940 g, was delivered with an Apgar score of 9 and 10 at 1 and 5 min, respectively.

A day after the delivery, treatment with bortezomib, lenalidomide, and dexamethasone was started. Five 28-day cycles were given resulting in very good partial response, with normalization of κ/λ ratio at the fourth cycle. Creatinine remained stable at 1.3 mg/dL. The patient proceeded with high-dose melphalan (200 mg/m^2) followed by autologous stem cell transplantation (ASCT) performed 8 months from diagnosis.

BM biopsy at day 87 post-ASCT was normocellular for age with polyclonal plasma cells comprising up to 5% of the BM cell population. The patient achieved stringent complete response (sCR) 3 months post-ASCT, and lenalidomide maintenance therapy was started and continues to date with stable sCR.

Discussion

The incidence of MM during pregnancy is uncommon. To date, 45 cases (including the present case) of MM, diagnosed around or during pregnancy, have been reported in the literature (Tables 1 and 2).[2,4–33] These cases included patients aged 21–43 years diagnosed before conception, during pregnancy, and up to 3 months after delivery. Eight patients were diagnosed before they had conceived:[6,7,13,15,25,29,31,32] five of them had active MM when they concei ved,[7,25,29,31,32] one had a known monoclonal gammopathy of undetermined significance (MGUS) about 6 years before pregnancy, stable MGUS/smoldering MM during pregnancy and progressive active MM in the postpartum period.[6] Two patients were in remission but the disease had relapsed during the pregnancy.[13,15] Thirty-three patients were diagnosed during pregnancy: 7 during the first trimester,[6,9,17,19] 15 (including the present case) during the second trimester,[2,4,5,8–11,13,16,22,26,33] and 11 during the third trimester. Five patients were diagnosed in the postpartum period.[13,21,27,28] FISH and cytogenetic analysis were reported in a minority of patients, and no published data were available for analysis.

As summarized in Table 2, all five patients with an active disease were treated with an anti-myeloma agent before pregnancy;[7,25,29,31,32] four of them were treated with these agents during the first trimester until the pregnancy was confirmed.[7,25,28,31] Sixteen patients received treatment for multiple myeloma during their pregnancy: seven with steroids only[2,6,10,11,16] and the remaining nine patients with various therapies.[4,9,29] Twelve patients were not treated during their pregnancy, most of them due to their request not to be treated while pregnant. Thirty-two of 45 patients were treated with anti-myeloma therapy after delivery or pregnancy termination.[2,5–8,10,11,13–20,22–24,26,27,29,31–33]

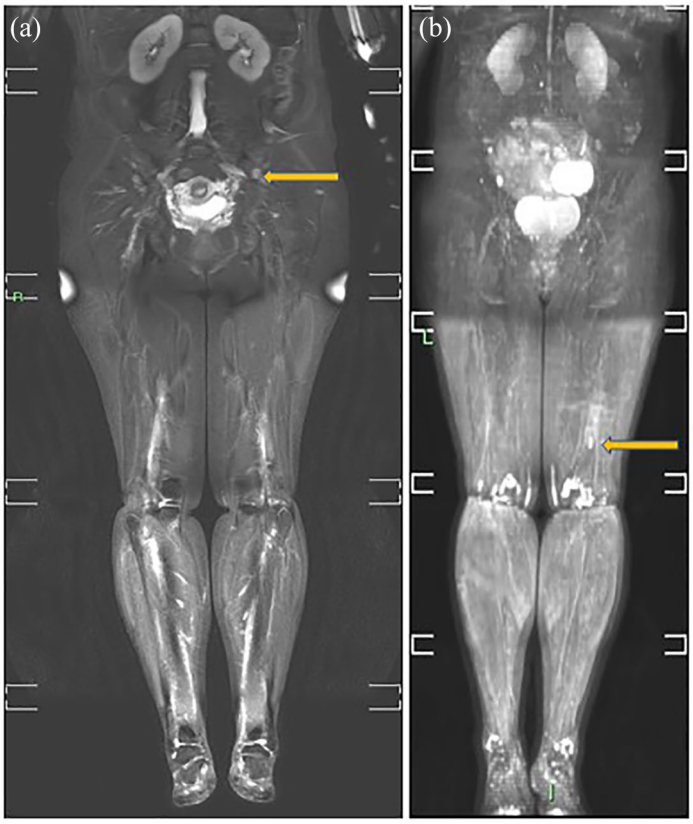

Figure 1. Whole-body MRI performed at 25 weeks of pregnancy. (a) 17 × 13 mm focal lesion in the left ileum wing, and tiny lesions in the ileum bones; (b) heterogenic bone marrow along the thighs which is particularly pronounced in the right distal thigh.

Forty-one women gave birth to 42 healthy babies, including a pair of twins. One patient had progressive disease and died after delivery. One newborn had an Apgar score of 5, which was followed by an uncomplicated neonatal course,[12] and another had seizures at birth that were related to difficulties with calcium regulation, but was healthy at

Table 1. Summary of case reports on multiple myeloma in pregnancy (including the present report).

	Reference	Symptoms	Age at diagnosis (years)	GA at diagnosis	MM subtype	Durie & Salmon	ISS	Treatment			GA at delivery	Fetal/ neonatal status
								Before pregnancy	During pregnancy	Postpartum		
1	Giordano[4]	Bone pain	40	Second trimester	NR	III	NR	–	CTX	Unknown	38 weeks	Healthy
2	Kosova and Schwartz[32]	Bone pain in lower back and hips	35	Before conception	NR	III	NR	RT + urethane	Urethane (until 6 weeks of gestation)	CTX	9 months	Healthy
3	Rosner *et al.*[31]	Bone pain, headaches	42	Before conception	NR	IIA	NR	Urethane	Urethane (until confirmation of pregnancy)	Urethane; chlorambucil, prednisone; melphalan	NR; Spontaneous birth	Healthy
4	Talerman *et al.*[30]	Jaundice, anemia	39	Third trimester	NR	IIA	NR	–	None	None	35	Healthy
5	Lergier *et al.*[29]	Generalized bone pain	21	Before conception	IgG	III	NR	MP; oxy-metholone; CTX	CTX	CTX	Full term	Healthy
6	Harster and Krause[28]	Lethargy, hypercalcemia, anemia	29	Postpartum	NR	III	NR	–	–	NR	NR	Healthy
7		Bone pain	30	Postpartum	IgG κ	III	NR	–	–	NR	NR	Healthy
8	Caudle *et al.*[33]	Anemia	33	20 weeks (second trimester)	IgG κ	IIB	NR	–	None	MP	38 weeks	Healthy
9	Malee[27]	Anemia, bone pain, right optic neuropathy, proximal lower extremity weakness, decreased response to pinprick beginning at thoracic level 4	32	Postpartum	IgA κ	IIIA	NR	–	–	MP; RT; cytoxan, 1–3-bis (2-chloroethyl)1-nirosourea, vincristine, MP	Not reported	Healthy
10	Pajor *et al.*[26]	Refractory anemia	27	16 weeks (second trimester)	IgG λ	IIA	NR	–	None	Non-recombinant human IFN α; vincristine, melphalan, meth-ylprednisolone	39 weeks	Healthy
11	Sakata *et al.*[25]	Anemia	38	Before conception	Light λ chains	IIIB	NR	Vincristine, doxorubicin, dexamethasone; IFN α	IFN α until 7 weeks gestation	None	38 weeks	Healthy
12	Maglione *et al.*[19]	Admitted for risk of miscarriage	34	6 weeks (first trimester)	Light λ chains	IIA	I	–	None	Thalidomide, chemotherapy; autologous and allogeneic bone marrow transplantation.	34	Healthy

(Continued)

Table 1. (Continued)

	Reference	Symptoms	Age at diagnosis (years)	GA at diagnosis	MM subtype	Durie & Salmon	ISS	Treatment			GA at delivery	Fetal/ neonatal status
								Before pregnancy	During pregnancy	Postpartum		
13	Forthman *et al.*[23]	Bone pain, anemia	41	28 weeks (third trimester)	Light λ chains	IIIB	NR	–	None	HDM with peripheral ASCT	34	Healthy, except for seizures at birth that were related to difficulties with calcium regulation
14	Malik *et al.*[22]	Excessive vomiting, light headedness, lethargy	34	15 weeks (second trimester)	IgG λ	IIIB	NR	–	None	VAD; external beam RT; CTX, thalidomide, dexamethasone	–	Pregnancy was terminated at 19 weeks
15	Lee *et al.*[21]	Diagnosed with monoclonal gammopathy of undetermined significance (MGUS) 5 years prior to conception. Postpartum: Increased lethargy, reduced appetite, nausea and vomiting, weight loss and back pain, renal failure.	**32**	Postpartum	IgG λ	IIIB	NR	–	–	–	Not reported	Healthy
16	Zun and Choi[24]	Back pain	32	31 weeks/third trimester	IgG λ	IIIB	II	–	–	First line: VAD; second line: VTD	32 weeks	Healthy
17	Quinn *et al.*[20]	Back pain, urinary retention, bilateral lower limb weakness	39	32 weeks/third trimester	IgG λ	IIIA	I	–	–	First line: ID; second line: ESHAP followed by high-dose therapy with PBSC rescue; third line: VD	32 weeks	Healthy
18	Dabrowska *et al.*[18]	Hypertension, anemia, proteinuria	42	28 weeks (third trimester)	IgA κ	II	I	–	–	Chemotherapy; ASCT	35 weeks	Healthy twins
19	Willmott *et al.*[10]	Bone pain, anemia, thrombocytopenia	33	15 weeks (second trimester)	Light chain only plasma cell myeloma	NR	I	–	Dexamethasone	CTD followed by HDM and PBSC rescue	33 weeks	Healthy
20	Rodriguez *et al.*[8]	Asthenia, hyperemesis, anemia, bone pain	31	18 weeks (second trimester)	IgA λ	III	NR	–	–	Vincristine, doxorubicin, dexamethasone followed by IFN α	–	Pregnancy was terminated

(Continued)

Table 1. (Continued)

	Reference	Symptoms	Age at diagnosis (years)	GA at diagnosis	MM subtype	Durie & Salmon	ISS	Treatment			GA at delivery	Fetal/ neonatal status
								Before pregnancy	During pregnancy	Postpartum		
21	Kasenda *et al.*[2]	Lower back pain, anemia	34	23 weeks (second trimester)	Light κ chains	IIIA	I	–	Prednisolone	VCD; followed by IVE mobilization and tandem PBSC transplantation after HDM	32 weeks	Healthy
22	Aviles and Neri[9]	NR	32	First trimester	NR	NR	NR	–	CTX, MP, vincristine; MP[a]	NR	36	Healthy
23		NR	37	Second trimester	NR	NR	NR	–	CTX, MP, vincristine, dexamethasone; MP[a]	NR	38	Healthy
24		NR	24	First trimester	NR	NR	NR	–	CTX, MP, vincristine, IFN α; MP[a]	NR	33	Healthy
25		NR	35	First trimester	NR	NR	NR	–	DHI MP[a]	NR	34	Healthy
26		NR	39	Second trimester	NR	NR	NR	–	DHI[a]	NR	38	Healthy
27		Severe anemia, renal insufficiency, fracture of the femur and vertebral collapse	32	Third trimester	NR	NR	NR	–	CTX, MP, vincristine[a]	NR	39	Healthy
28	Borja de Mozota *et al.*[17]	Asymptomatic proteinuria	33	12 weeks (first trimester)	IgG κ	NR	NR	–	None	VD followed by HDM, double ASCT; lenalidomide maintenance treatment	34	Healthy
29	Brisou *et al.*[15]	Relapse during pregnancy: Low back pain, anemia	26 (initial diagnosis – 12 years prior to conception) 38 (relapse during pregnancy)	Initial diagnosis 12 years prior to conception. Relapse at 7 months of pregnancy (third trimester)	Light κ chains	IIA	NR	First line: VAD (vincristine, doxorubicin, dexamethasone), pamidronate, radiotherapy. Second line: VAD followed by high-dose cyclophos-phamide, double autologous stem cell transplant after high-dose melphalan	None	VCD	37	Healthy
30	Bouzguenda *et al.*[16]	Bilateral breast lumps	39	26 weeks (second trimester)	IgG λ	IIIA	II	–	Dexamethasone	TD, external beam RT	34	Healthy
31	Smith *et al.*[11]	Proteinuria, anemia	34	24 weeks (second trimester)	Light κ chains	IIIA	I	–	Dexamethasone	VD; HDM, ASCT	35	Healthy
32		Back pain, leg weakness, decreased sensation and difficulty voiding urine	38	32 (Third trimester)	IgG λ	IIIA	I	–	–	Dexamethasone; RT; ICD; ESHAP; ASCT; VD; RD	32	Healthy

(Continued)

Table 1. (Continued)

	Reference	Symptoms	Age at diagnosis (years)	GA at diagnosis	MM subtype	Durie & Salmon	ISS	Treatment			GA at delivery	Fetal/ neonatal status
								Before pregnancy	During pregnancy	Postpartum		
33		Cytopenia, hypercalcemia	33	14 weeks (second trimester)	Light λ chains	IIIA	I	–	Dexamethasone	RT, CTD; HDM, ASCT; VAD; lenalidomide	33	Healthy
34	Khot *et al.*[13]	Persistent hemorrhage after spontaneous abortion	30	Postpartum	IgD λ	NR	I	–	–	Vincristine, doxorubicin, dexamethasone; HPC harvest after CTX and rh-GCSF mobilization; autologous HPC transplant after HDM; intravenous bisphosphonate therapy	NR	Spontaneous abortion
			37	Relapse during pregnancy				The patient was in complete response for 5 years	–	RD	NR	Healthy
35		NR	32	14 weeks (second trimester)	Light κ chains	III	I	–	–	VAD, RT; vincristine, liposomal doxorubicin, dexamethasone; high-dose CTX, dexamethasone, HDM conditioned autologous HPC transplant; MUC-1 loaded dendritic cell injections, investigational therapy with a VEGF inhibitor, pazopanib, bortezomib dexamethasone; bortezomib, romidepsin, dexamethasone; thalidomide; VCD	NR	Pregnancy termination
36	McIntosh *et al.*[12]	Epigastric pain, nausea, vomiting, rib and back pain, pancreatitis	22	32 weeks (third trimester)	Light κ chain	IIIB	I	–	–	NR	32	Apgar 5, followed by uncomplicated neonatal course
37	Cabanas-Perianes *et al.*[14]	Anemia	37	27 weeks (third trimester)	IgG λ	IIIA	II	–	None	VRD	34	Healthy

(Continued)

Table 1. (Continued)

	Reference	Symptoms	Age at diagnosis (years)	GA at diagnosis	MM subtype	Durie & Salmon	ISS	Treatment			GA at delivery	Fetal/ neonatal status
								Before pregnancy	During pregnancy	Postpartum		
38	Jurczyszyn *et al.*[6]	Rib fractures, anemia, hypercalcemia associated with acute renal failure	43	28 weeks (third semester)	Light κ chain	IIIB	III	–	high-dose methylprednisolone	VD; bortezomib, pomalidomide	30	Healthy
39		Back pain	39	31 weeks (third trimester)	IgA λ	IIIA	I	–	Dexamethasone	VD; autologous PBSC transplant; RD; VRD; pomalidomide, dexamethasone	36	Healthy
40		Mild cytopenias	34	Before conception	Smoldering myeloma; IgG λ	IA	I	–	None	Yes (treatment details were not specified)	NR	Healthy
41		NR	NR	First trimester	Solitary plasmacytoma	IA	II	–	None	Yes (treatment details were not specified)	NR	Healthy
42		NR	NR	First trimester	IgG λ	IIIA	I	–	None	Yes (treatment details were not specified)	NR	Healthy
43	Kim *et al.*[5]	Abdominal distention, lower extremity pitting edema, proteinuria	34	20 weeks (second trimester)	Light chain deposition disease	NR	NR	–	–	VTD	24 weeks	Stillborn
44	Garg *et al.*[7]	Progressive weakness and backache	29	Before conception	IgG κ	NR	NR	Vincristine, doxorubicin, dexamethasone; TD	TD (stopped at 12 weeks of gestation)	VCD; ASCT	37 weeks	Healthy
45	Present case	Hypertension, acute renal failure	40	16 weeks (second trimester)	IgG κ	–	Revised ISS II	–	HDD; CTX and HDD	VRD; HDM, ASCT; lenalidomide	36 weeks	Healthy

ASCT, autologous stem cell transplantation; CMOP, cyclophosphamide, melphalan, vincristine, prednisone; CTD, cyclophosphamide, thalidomide, dexamethasone; CTX, cyclophosphamide; DHI, double hemibody irradiation; ESHAP, etoposide, cisplatin, cytarabine, methylprednisolone; GA, gestational age; HDD, high-dose dexamethasone; HDM, high-dose melphalan; HPC, hematopoietic progenitor cell; ICD, idarubucin, cyclophosphamide, dexamethasone; ID, idarubucin, dexamethasone; IFN, interferon alpha; ISS, International Staging System; IVE, ifosfamide, epirubicin, etoposide; MGUS, monoclonal gammopathy of undetermined significance; MM, multiple myeloma; MP, melphalan, prednisone; MUC-1, Mucin 1, cell surface associated; NR, not reported; PBSC, peripheral blood stem cells; RD, lenalidomide, dexamethasone; rh-GCSF, recombinant human granulocyte colony-stimulating factor; RT, radiotherapy; TD, thalidomide, dexamethasone; VAD, bortezomib, doxorubicin, dexamethasone; VCD, bortezomib, cyclophosphamide, dexamethasone; VD, bortezomib, dexamethasone; VEGF, vascular endothelial growth factor; VRD, bortezomib, lenalidomide, dexamethasone; VTD, bortezomib, thalidomide, dexamethasone.

[a]Chemotherapy was stopped 3–4 weeks before delivery to avoid hematological toxicity in the newborn.

Table 2. Summary of the demographic and clinical characteristics of cases of multiple myeloma in pregnancy (including the present report).

Parameter	Case reports *N* = 45
Age, years	21–43
Diagnosis of multiple myeloma	
Before conception	8 (5 with active disease; one had smoldering myeloma; 2 experienced a relapse during pregnancy)
During pregnancy	32
First trimester	7
Second trimester	15
Third trimester	11
Postpartum	5
After delivery of a healthy baby	4
After spontaneous abortion	1
Multiple myeloma subtype	
IgG λ	10
IgA λ	2
IgD λ	1
Light λ chains	4
Light κ chains	5
IgG κ	5
IgA κ	2
IgG	1
Plasma cell myeloma	1
Solitary plasmacytoma	1
Light chain deposition disease of λ type	1
Not reported	11
Durie-Salmon Classification	
IA	2
II	1
IIA	5
IIB	1
III	7
IIIA	10
IIIB	7
Not evaluated	11
International Staging System (ISS)	
I	14
II	4
III	1
Not reported	25
Revised ISS score	
II	1
Treatment	
Before pregnancy	5
During pregnancy	20
Dexamethasone	5
Cyclophosphamide	2
Urethane	2 (one until GA 6 weeks, one until pregnancy confirmation)
Prednisolone	1
Methylprednisolone	1
Dexamethasone, cyclophosphamide	1
CMOP, MP	1
CMOP, doxorubicin, MP	1
CMOP, Interferon α, MP	1
Double hemibody irradiation, MP	1
Double hemibody irradiation	1
CMOP	1
Interferon α	1 (until GA 7 weeks)
Thalidomide, dexamethasone	1 (until GA 12 weeks)
Not treated during the pregnancy	12
Postpartum	33
Neonatal status	
Healthy	41
Pregnancy termination	3
Spontaneous abortion	1
Stillbirth	1
Unknown status	1

CMOP, cyclophosphamide, melphalan, vincristine, prednisone; GA, gestational age; ISS, International Staging System; MP, melphalan, prednisone.

follow-up.[23] Three pregnancies were terminated.[8,13,22] One women had a spontaneous abortion, after which MM was diagnosed; the women gave birth to a healthy baby 5 years later, despite a relapse of the disease during the pregnancy.[13]

Due to the low prevalence of MM in young adults, the initial investigation of the underlying causes of the patient's symptoms – hypertension and acute renal failure – was directed toward pregnancy-related disorders, such as iron deficiency, preeclampsia, or primary kidney disorder, delaying the initial diagnosis. Once diagnosis was determined, treatment was initiated in order to delay disease progression and further damage to target organs while maintaining the safety of the fetus. The therapy regimen included CTX and HDD which enabled the completion of the pregnancy and the delivery of a healthy baby.

Treating physicians should be aware of potential effects of MM therapies on the fetus and pregnancy outcomes. Table 3 summarizes the limited evidence on the safety of the major classes of MM therapies during pregnancy. Most anti-MM agents have shown embryo lethality or teratogenicity when given during pregnancy in animal studies. Despite the widespread use of corticosteroids in MM protocols,[37] high-dose corticosteroids confer a slightly higher risk for fetal malformations in the first trimester, and a higher risk for obstetric complications in the second or third trimesters.[38–41] Prednisolone is the preferred steroid as it is metabolized by the placenta with only 10% of maternal dose reaching the fetus.[42] In the case described here, the patient received HDD and CTX. CTX was also administered to two other pregnant patients – one in the second trimester and one in the third – but did not affect

Table 3. Classification of multiple myeloma therapy by fetal risks.

Drug	Mechanism of action	Effect on fetus	FDA pregnancy categories[a]	Australian categorization system[b]
Corticosteroids	Broad anti-inflammatory and immunosuppressive activity.[37]	A marginally increased risk of major malformations after first-trimester exposure to corticosteroids. Increase by an order of 3.4-fold the risk of oral cleft,[41] preterm rupture of the fetal membranes,[39] effect on fetal hypothalamic-pituitary-adrenal axis development,[38] preterm birth, maternal diabetes.	A	A
Alkylating agents				
Cyclophosphamide	Alkylating agent. The phosphoramide mustard metabolite forms irreversible DNA cross-links between and within DNA strands at guanine N-7 positions, leading to cell apoptosis.[44]	Cyclophosphamide embryopathy, including growth restriction, ear and facial abnormalities, absence of digits and hypoplastic limbs.[45] Low-dose intravenous CTX therapy may not be hazardous to the fetus during late pregnancy.[43]	D	D
Melphalan	Alkylating agent. Nitrogen mustard analog. Targets actively dividing cells.[46]	Evidence of embryo lethality and teratogenicity when given during pregnancy in animal studies. Effects in humans are unknown.[46]	D	D

(Continued)

Table 3. (Continued)

Drug	Mechanism of action	Effect on fetus	FDA pregnancy categories[a]	Australian categorization system[b]
Immunomodulatory drugs				
Thalidomide and derivatives: lenalidomide, pomalidomide	Anti-proliferative and pro-apoptotic effects on malignant cells, immune regulatory function, interruption of tumor microenvironment interactions.[47]	Severe fetal defects and embryofetal deaths.[48]	Not assigned	X
Proteosome inhibitors				
Bortezomib	Inhibition of protein degradation through the ubiquitin-proteasome system thereby leading to accumulation of misfolded or unfolded proteins in plasma cells. The accumulated proteins produce activation of pro- and anti-proliferative signals, interfere with the cell cycle, and activate apoptotic pathways that lead to cell death.[49,50]	Embryo-fetal lethality in rabbits. Significant post-implantation loss and a reduced number of live fetuses. Live fetuses had significantly lower fetal weight.[51] No controlled data regarding the use of bortezomib in human pregnancies.	D	C
Carfilzomib		Embryo-fetal toxicity in rabbits. No teratogenicity in pregnant rats when the drug was administered during the organogenesis period (Note: carfilzomib exposure in animals was below the exposure achieved in humans).[51]	Not assigned	C
Ixazomib		Ixazomib caused embryo-fetal toxicity only at maternally toxic doses and at exposures that were slightly higher than those observed in patients receiving the recommended dose. In pregnant rabbits, increased fetal external abnormalities in the tail were observed at doses ⩾1.0 mg/kg, and skeletal variations/abnormalities were observed at doses ⩾0.3 mg/kg.[52]	Not assigned	C
Monoclonal antibodies				
Daratumumab	A humanized Ig G1-kappa mAb that targets CD38, a 46-kDa type II transmembrane glycoprotein broadly expressed on plasma cells.[53] Binding of daratumumab to CD38 induces myeloma cells death by several mechanisms including complement-dependent cytotoxicity (CDC), antibody-dependent cell-mediated cytotoxicity (ADCC), antibody-dependent cellular phagocytosis (ADCP), and apoptosis.[54]	IgG1 monoclonal antibodies cross the placenta after the first trimester of pregnancy and may cause fetal myeloid or lymphoid-cell depletion and decreased bone density.	Not assigned	C

(Continued)

Table 3. (Continued)

Drug	Mechanism of action	Effect on fetus	FDA pregnancy categories[a]	Australian categorization system[b]
Isatuximab,	An IgG1 monoclonal antibody that binds selectively to a specific epitope on the CD38 receptor. This binding can target tumor cells through a combination of mechanisms, including ADCC, ADCP, CDC, and immune cell depletion/inhibition of T regulatory cells.[55]	Animal reproduction studies have not been conducted with this drug.	Not assigned	C
Elotuzumab	Elotuzumab is a monoclonal antibody that primarily acts via ADCC and also by directly activating natural killer cells to kill myeloma cells.[56]	No data regarding use in pregnant animals or humans.	Not assigned	C

ADCC, antibody-dependent cell-mediated cytotoxicity; ADCP, antibody-dependent cellular phagocytosis; CDC, complement-dependent cytotoxicity; CTX, cyclophosphamide; FDA, Food and Drug Administration.
[a]Chemical Hazards Emergency Medical Management. FDA Pregnancy Categories. US Department of Health and Human Services. Available from: https://chemm.nlm.nih.gov/pregnancycategories.htm.
[b]Australian categorisation system for prescribing medicines in pregnancy. Australian Government Department of Health. Therapeutic Goods Administration. Available from: https://www.tga.gov.au/australian-categorisation-system-prescribing-medicines-pregnancy.

the development of the fetus.[4,29] Low-dose CTX administered to a patient with Burkitt's lymphoma during the third trimester showed good response with delivery of a normal baby, suggesting that low-dose intravenous CTX therapy may not be hazardous to the fetus during late pregnancy.[43]

In conclusion, despite the rarity of concurrent MM and pregnancy, this possibility should be considered in patients with signs and symptoms that may be attributed to MM so as not to delay the diagnosis and decision about pregnancy continuation and initiation of appropriate, safe, and efficient therapy.

Author contributions

Hila Magen: Data curation; Writing – original draft; Writing – review & editing.

Michal J. Simchen: Data curation; Writing – review & editing.

Shira Erman: Data curation.

Abraham Avigdor: Writing – review & editing.

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