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# Treatment of Multiple Myeloma During Pregnancy

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## 1. Abstract

**1.1. Objective:** To search longer follow-up in 9 mothers and newborn, whose received chemotherapy, even in first trimester, and analyze the risk of late adverse events, and the outcome in the mothers.

**1.2. Patients and Methods:** Retrospectively, we revised 9 cases of mother diagnosed and treated in our Institution, whose standard chemotherapy regimen, and after delivery, they continued the specific treatment, including autologous stem cell transplant. Newborns were evaluated to detect presence of late adverse events.

**1.3. Results:** Chemotherapy were well tolerated, without any severe toxicities, after delivery they continued the treatment, including 4 whose received autologous stem cell transplant. Neither show late adverse events. They were matched with 18 no pregnant patients with multiple myeloma, with the same age, stage, treatments, and the pregnant patients have a better progression- free survival and overall survival. The nine newborns had a normal evolution.

**1.4. Conclusion:** Pregnant mothers associated to multiple myeloma, appear to be will treated with adequate chemotherapy, because mothers and newborns, tolerated the treatment, without severe acute and late toxicities, additionally better outcome in mothers were observed

## 2. Introduction

Malignant neoplasms during pregnancy contribute to various problems as diagnostic, therapeutic decision to analyzed the less toxicity to mother and fetus, social; a need to be treated by an interdisciplinary approach; because most of these clinical situation need a quickly treatment; moreover, different aspects, such, as gestational state, age, stage of the neoplasm, risk to the fetus, and patient decision will be take in consideration. Based to recent dates, neoplasm during pregnancy is diagnosed approximately in 1: 1,000 pregnant women; with still increased due to rising median age at diagnosis. The most common are solid tumors: cervical cancer, melanoma and breast cancer. In hematological malignancies HM), Hodgkin lymphoma and diffuse large B-cell lymphoma are the most frequent of this clinical situations. Multiple Myeloma (MM) are most common in patients > 40 years old, thus the association of MM and pregnancy is very rare, 45 cases of this association has been reviewed in recent manuscripts [1-5], Moreover, most of this reports are single cases, with short follow-up of mother. Thus, adequate treatment has not been defined and the effects of pregnancy on the neoplasm has remain unknown. Some years ago, we report 6 cases of MM and pregnancy [3]; from 2009 to 2017 we diagnosed and treated three cases more. Thus, we analyzed the dates of the nine patients, including longer follow-up of children, and the impact in outcome of MM associated to pregnancy.

## 3. Patients and Methods

From 1993 to 2017, patients with pathological and laboratory were diagnostic as MM, and pregnancy was associated, they were send to the High-risk section of the Hematology department to evaluate the case. When pregnancy was confirmed, and expert obstetricians performed a evaluation of the mother and fetus, including ultrasound , every 4 weeks continue with the same program, at 32 weeks of pregnancy, the delivery form were evaluated, taking in consideration that all patients had lytic on pelvis and/or spine, delivery was for cesarean section Treatment of multiple myeloma

were according to the programs in our institution, including Autologous Stem Cell Transplant (ASCT) [6,7], and the administration of chemotherapy was stopped at 34 to 36 weeks, to avoid the risk of granulocytopenia in the newborn. At delivery the newborn was careful evaluated by an expert neonatologist to detect congenital malformations, complete blood count, serum chemistry, protein electrophoresis, serum determinations of Beta 2 microglobulin, lactate dehydrogenase, and karyotype. The newborns were evaluated every 6 months, until 3 years, annually 3 to 18 years. Weight and height, physical development, scholar learning, social development, laboratory test, including beta 2 microglobulin, protein electrophoresis determination of light chain in blood and urine. Mothers, continue treatment according with the myeloma status. Until now, no definitive rules to continued myeloma treatment, when they were in complete response, thus, we decided to stop any specific treatment if the patient has more of 5-years in complete response, but, we continue with the follow-up, until relapse or die from any cause. Before start treatment, patient and spouse, were informed about the risks to begin chemotherapy, the risk of patient a fetus, they received, scientific support (second opinion), legal assistance: and signed and consent form. The treatment was approved the Ethical and Scientific Committee. Statistical Analysis, taking in consideration the low number of patients it was not performed.

## 4. Results

(Table 1) show the clinical characteristics, treatment, during pregnancy and after it, and the current status. Median age was 33 years (range :24 to 39), five patients were in the firsts trimester of pregnancy, but all were symptomatic and advance disease, thus after discussion, we decided specific treatment. In all cases tolerance to chemotherapy were well tolerated, no acute toxicities were observed, at the delivery time, five were in complete response, furthermore, they completed the program of treatment including ASCT, as observed, five patients are alive, 10 to > 15 years after delivery. We matched this group of patients with a control group of 18 no-pregnant women, with multiple myeloma, stage, clinical risk, treatment (including ASCT), to evaluate outcome, in pregnant patients , progression-free survival at 5-years were 4.5 years that were better compared with the control group: 3.2 years, also OS were better in pregnant patients 8.9 (4,5 to > 15 ) years compared to matched group 5.6 (2-10)years .But, the groups were small to performed an statistical analysis .The newborns did not show any congenital malformations, serum beta 2 microglobulin, electrophoresis of protein and light- chain in serum an urine. Clinical development, weight and height, scholar attendance, social, neurological development were similar to children of the same age, socio-economic were similar [8, 9]. Until now, no late toxicities have been observed.

**Table 1:** Mothers, treatment during pregnancy

| Age | Trimester * | Treatment | Delivery (week)/weight | Follow-up |
|---|---|---|---|---|
| 32 | 1 | CMOP (6 **) | 36/2900 | ASCT |
| | | | | Relapse: 4.1 years*** |
| | | | | 2a line: CR |
| | | | | Relapse: no response |
| | | | | Palliative |
| | | | | Die : 3.2 years*** |
| | | | | OS: 7.6 years *** |
| 37 | 2 | CMOP ( 3**) | 38/3100 | PR: ASCT : CR |
| | | | | Relapse: 2.8 years*** |
| | | | | 2a line:PR(2.1years***) |
| | | | | relapse: Third line |
| | | | | Progression : die |
| | | | | OS: 6.2 years *** |
| 24 | 1 | CMOP +I (3) | 33/2850 | CR |
| | | | | Maintenance: |
| | | | | Progression: 3.7years*** |
| | | | | Relapse: ASCT |
| | | | | 6.4 ***years |
| | | | | Relapse : 2a line: |
| | | | | CR: 3.0*** |
| | | | | Alive years |

| | | | | |
|---|---|---|---|---|
| | | | | 14.*** |
| 35 | 1 | (DAI ,6**) | 39/2500 | CR: 5.1 *** |
| | | | | Relapse: ASCT :4.2 years *** |
| | | | | Maintenance : 3.5 years |
| | | | | Alive OS: 17 years **** |
| 39 | 2 | (DAI, 6 ***) | 38 /2750 | ASCT (5.9 years **) |
| | | | | Relapse : 2a line |
| | | | | PR 3.4 years *** |
| | | | | Progression |
| | | | | Die, OS: 10 years *** |
| 32 | 3 | (CMOP, 3 ***) | 39/3050 | CMOP x 3, ASCT, CR |
| | | | | Maintenance 4.7 years**** |
| | | | | Relapse |
| | | | | 2a line :CR: 3.3 years *** |
| | | | | Alive, OS: 10 years**** |
| 33 | 1 | (DAI, 6) | 37 (3100) | ASCT: 6.1 years *** |
| | | | | Relapse: 2a line: CR |
| | | | | Maintenance: 2.2 years |
| | | | | Alive , OS: 8.9 *** |
| 28 | 2 | (DAI, 5) | 39/3100 | ASCT: 5.1 *** |
| | | | | Relapse: 2a line |
| | | | | CR: 2.3 years *** |
| | | | | Relapse: 3a line: 2a CR , maintenance 2 years , Alive OS 9.3 years **** |
| 30 | 1 | (DAI, 6**) | | Failure, ASCT, PR |
| | | | | 1.8 years Progression |
| | | | | Die. OS 2.6 years |

Trimester when chemotherapy was initially, ** Number of cycles during all pregnancy, *** Response achieved with the specific treatment ; *** * duration survival after pregnancy: 2a line: thalidomide, dexamethasone and cyclophosphamide

ASCT : autologous stem cell transplant and treatment administered ,

Abbreviations: CMOP: cyclophosphamide , melphalan, vincristine, prednisone, (***,number total of cycles during pregnancy) DAI (dexamethasone, all trans retinoic acid, interferon)

***Duration of response of these phase of treatment), PR: partial response, CR: complete response, 2a line: dexamethasone, thalidomide, melphalan; ASCT: autologous stem cell transplant , 3a line: Bortezomib, dexamethasone **** (duration of survival from diagnosis to death)

## 5. Discussion

We present a retrospective analysis of nine patients with a rare presentation: pregnancy during MM treatment, we observe that the chemotherapy employed in this cases were well tolerated, excessive toxicities were not observed, the obstetrical outcome was similar compared with non-pregnant myeloma treated with the same chemotherapy, response was excellent, and before delivery the patients can have continued with the treatment, including ASCT. The newborns did not show any congenital malformations, the physical, social, scholar development were normal, according to the Mexican tables. Moreover, surprisingly, mothers treated with chemotherapy during pregnancy have an better survival compared with a matched group.

Taking in consideration that these association is very rare, an until now only 46 cases has been reported, define the best treatment is very difficult. Recent revisions show that most cases, (15, 33%) were diagnosed during second trimester, when the fetus have minor risk of development severe damage. Seven were diagnosed during first trimester, buy, they did not receive aggressive treatment, most cases received steroids, at low doses, some cases received low doses of alkylant agents. Thus, neither of these cases never received an aggressive treatment. In our cases, MM have higher clinical risk, multiple lytic lesions, and severe cytopenias and we decide to begin treatment; based in our experience with another hematological malignancies, acute leukemia, aggressive lymphoma and advanced stages Hodgkin lymphoma, were treated with aggressive chemotherapy [7] after clinical and legal considerations, began combined chemotherapy, some with cyclophosphamide and melphalan, and most with biological agents. As mentioned, follow-up of children and newborns is excellent, five patients are alive, three for more than 10 years. Several studies have been reported the

metabolism of cytotoxic drugs during pregnancy, but, the drugs employed in patients with MM, only cyclophosphamide has been studied. In all cases, serum concentrations in fetus are significantly minors that maternal serum. Moreover, multiple physiological changes during pregnancy can help to diminished the risk for the fetus [10]. Obviously no definitive conclusions can be performed, but, in our study we show that combined chemotherapy is feasible, well tolerated and without excessive risks to mother and fetus. We suggested that every case of this associated will be reported to obtained an major number of cases and define an adequate treatment.

## 6. Authors Contributions

Both authors contributed equally to this manuscript, design the study, collection data, performed data and wrote the manuscript.

## 7. Conflict of Interest

Both authors disclose any conflict of interest.

## 8. Data Available

The data that support the findings of this study are available from the corresponding author, upon reasonable request.

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