MJoSHT
Malaysian Journal of Science, Health & Technology
[mjosht.usim.edu.my]

USIM

Article

Case Series of Acute Myeloid Leukemia (AML) in Pregnancy – A Single Centre Experience over 5 years Review

Emily C. D'Silva[1], Rui Jeat Fann[2], Lim Kar Koong[1], Jameela Sathar[2]

[1]*Department of Obstetrics & Gynaecology, Hospital Ampang, Ampang Jaya, 68000, Malaysia.*
[2]*Department of Haematology, Hospital Ampang, Ampang Jaya, 68000, Malaysia.*

Correspondence should be addressed to:
Emily C. D'Silva; ppemilyhpj@gmail.com

Article Info
Article history:
Received:26 April 2022
Accepted:14 October 2022
Published:6 April 2023

Academic Editor:
Norsham Juliana

Malaysian Journal of Science, Health & Technology

MJoSHT2023, Volume 9, Issue No. 1
eISSN: 2601-0003

https://doi.org/10.33102/mjosht.v9i1.269

***Abstract*— Acute Myeloid Leukemia (AML) is a rare condition presenting in pregnancy and still poses a challenge in its management which involves maintaining a balance between maternal and fetal well-being. This study aims to create a local registry for haematological malignancy in pregnancy and to review outcomes of both maternal and fetal outcome. Twelve pregnancies were identified from 11 patients. 3 pregnancies were terminated upon diagnosis and 1 miscarried. One maternal death prior to decision. Out of the 6 pregnancies continued, 5 received chemotherapy during pregnancy with all successfully achieving complete remission and were delivered at 33-37 weeks gestation. All babies delivered with good Apgar score with 1 reported neonatal death. One fetal anomaly reported in a patient exposed to Decitabine in early pregnancy. Chemotherapy can be safely administered during second or third trimester with delivery planned as close to term as possible. Decitabine should be avoided during pregnancy due to its potential teratogenicity.**

***Keywords*—** Acute myeloid leukemia; pregnancy; maternal outcome; fetal outcome.

I. INTRODUCTION

Acute myeloid leukemia (AML) is a rare condition presenting in pregnancy and poses a challenge in management. Its management involves striking a balance in maintaining the well-being of both the mother with least harm to the fetus. Historically, recommendations in managing these patients are based on retrospective studies with small sample size and case reports due to its rarity.

Western country registry for acute leukemia shows an incidence of 1 in 75,000 to 100,000 pregnancies, where two thirds of these are AML [1]. At present, the International Network of Cancer, Infertility and Pregnancy (INCIP) is the largest known registry that has collaboration from 25 countries which looks into combined data from both oncology and obstetrics [2]. According to the registry, haematological cancer is the second most common cancer during pregnancy with leukemia being the 4th amongst it [2].

The availability of a sufficient large data enables evidenced-based recommendation for health-care workers to provide a balanced and holistic care plan in managing this delicate condition. Factors such as type and sub-type of malignancy, gestational age at diagnosis, aggressiveness of the disease, condition of both maternal and fetus at point of

diagnosis and through-out pregnancy, as well as tumour burden needs to be considered on formulating a care plan.

In Malaysia, there is no local registry for haematological malignancy in pregnancy. Data on occurrence of haematological malignancy and pregnancy outcome including post-delivery maternal and fetal outcome are still lacking in our local setting. Due to demographic and cultural differences between the west and Malaysia, it would be an advantage to be able to extract data from our own local registry that can represent our unique local population.

Ampang Hospital is the national reference centre for haematological diseases in Malaysia. This study aims to review data on the outcome of both maternal and fetal of pregnant women with AML in Ampang Hospital. We would also like to look at the treatment strategies used in Ampang Hospital in managing AML in pregnancy and provide useful recommendations pertaining to its management base on our local data. We also aim to set-up a local registry and contribute data to improve our understanding of haematological malignancy, namely AML in pregnancy in our local setting.

II. METHOD AND MATERIAL

This is a retrospective study of all patients we have encountered at our centre with AML during pregnancy who were diagnosed and managed at our centre between 1 January 2014 to 31 December 2018. Patients who were diagnosed with AML were identified from the delivery registry and obstetrics clinic registry. Clinical data including patient demographics, investigations, diagnosis, treatment regimens were collected. Data on pregnancy outcome of both mother and fetus were carefully extracted from the hospital electronic records.

III. RESULTS

A total of 12 pregnancies from 11 patients were identified with 2 of the pregnancies originating from the same patient (cases 6 and 7). Two were patients who conceived while receiving chemotherapy. The remaining 9 patients (82%) were newly diagnosed AML during pregnancy (Table 1).

Two patients were asymptomatic and was referred due to pancytopenia and neutropenia from routine antenatal blood investigation done in primary health facilities. One patient with previously treated Burkitt Lymphoma was diagnosed to have therapy related AML as a result from previous treatment received quite distant in the past. The remaining 8 patients presented with anemic symptoms, bleeding, and fever (Table 1). All the cases underwent an uncomplicated bone marrow aspiration and trephine biopsy (BMAT) during pregnancy, except 2 cases which was deferred after termination of pregnancy. This strongly supports the notion that pregnancy should not be a hinderance to BMAT.

Two pregnancies (17%) resulted in both maternal and fetal demise in second trimester due to advanced disease. Three pregnancies (25%) were terminated upon diagnosis after detailed discussion with the couple at 7 weeks, 19 weeks, and 22 weeks respectively for initiation of chemotherapy and fetal anomaly. One pregnancy miscarried at 9 weeks of gestation (Figure 1&2).

Five pregnancies (42%) were continued and received antenatal chemotherapy in the second trimester. One pregnancy was planned for chemotherapy post-delivery as the diagnosis was made at 36 weeks gestation because of late presentation. She had an uncomplicated delivery at 36 weeks for obstetrics indication with birthweight of 2470g followed by post-natal chemotherapy. Treatment regime at our center include cytarabine-daunorubicin, high dose cytarabine, and idarubicin. All 5 pregnancies who received antenatal chemotherapy delivered between 33-37 weeks of gestation with birthweight 1600-2250g (Table 3). Mode of delivery included 2 caesarean deliveries for fetal distress and 4 vaginal deliveries. All babies had good Apgar score at delivery except for 1 lost data. There is 1 reported neonatal death at day 19 of life secondary to neutropenic sepsis with multi-organ failure. This patient received high dose cytarabine during pregnancy.

Chemotherapy was started in the second trimester as early as 24 weeks gestation after counselling (Table 2). These patients were followed-up and all achieved complete post-induction remission. Postnatal complications included 1 caesarean wound breakdown requiring secondary suturing and 4 neutropenic sepsis which resolved with in-patient management and antibiotics. The antibiotic regime given as per our local neutropenic sepsis protocol which includes broad spectrum with pseudomonas coverage.

One case of multiple fetal anomaly which was lethal (holoprosencephaly, absence nasal bone, cleft lip) was reported in a patient exposed to decitabine in early pregnancy in which the pregnancy was terminated at 19 weeks of gestation and chemotherapy continued post termination.

There were 3 maternal deaths (27%), encountered during this period. One had termination of pregnancy but succumbed due to refractory disease while the other 2 involved both maternal and fetal demise at second trimester due to advanced disease.

Table 1. Patient's Demographic, Symptoms at Presentation and Diagnosis over 5 years Review

Case	Age	Co-morbids	Gestation week at diagnosis (month/year)	Presenting symptoms	Investigation at presentation (TWC/Hb/Plt)	Disease status	Cytogenetics
1	19	Substance abuse	24 (July/2014)	Anemia	1.1/4.5/57	Newly diagnosed	t(15:17)
2	25	NIL	36 (Oct/2014)	Bleeding	8.8/7.4/21	Newly diagnosed	t(15:17)
3	32	NIL	22 (Nov/2014)	NIL	2.5/11.8/155	Newly diagnosed	Not further classified
4	27	NIL	19 (Jan/2015)	Bleeding	10.4/7.9/103	Newly diagnosed	CBFB-MYH
5	31	Burkitt Lymphoma	21 (Mar/2015)	NIL	246/8.3/35	Newly diagnosed	Not further classified
***6**	24	NIL	N/A (Jun/2015)	NIL	9.4/12.8/194	Previously diagnosed on treatment	Inv(16)
***7**	25	NIL	16 (May/2016)	Fever, bleeding	6.9/12.5/51	Relapsed disease	Inv(16)
8	32	Hepatitis B	25 (Jan/2017)	Anemia	4.2/8.7/66	Newly diagnosed	Not further classified
9	36	Obesity, PIH	16 (Aug/2016)	NIL	2.9/6.9/34	Newly diagnosed	Not further classified
10	26	APLS	9 (Jan/2017)	Bleeding	5.2/8.9/7	Newly diagnosed	Not further classified
11	39	Hepatitis B	N/A (Jun/2017)	NIL	4.1/13.1/159	Previously diagnosed on treatment	FLT 3 positive
12	32	NIL	24 (Dec/2018)	Bleeding	6/5/26	Newly diagnosed	Not further classified

Dx, diagnosis; TWC, total white cell count (x10^3/uL); Hb, hemoglobin (g/dL); Plt, platelet counts (x10^3/uL); PIH, pregnancy induced hypertension; APLS, anti-phospholipid syndrome; N/A, not applicable; t(15:17), chromosomal translocation t(15;17)(q22;q21); CBFB-MYH, core-binding factor subunit Beta -mutY DNA glycosidase gene rearrangement; Inv(16), chromosomal inversion of chromosome 16; FLT 3, Fms related receptor tyrosine kinase 3.
**same patient.*

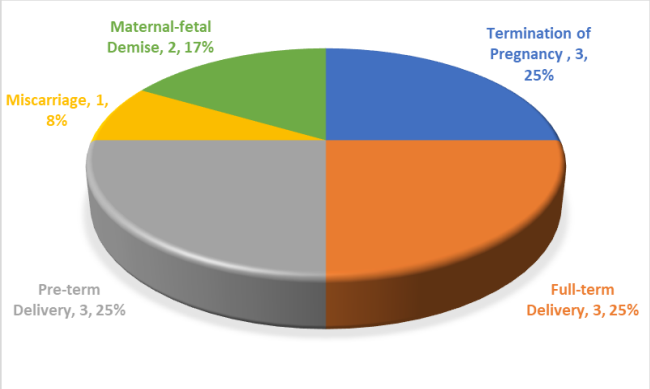

Figure 1. Pregnancy Outcome with Acute Myeloid Leukemia over 5 years Review

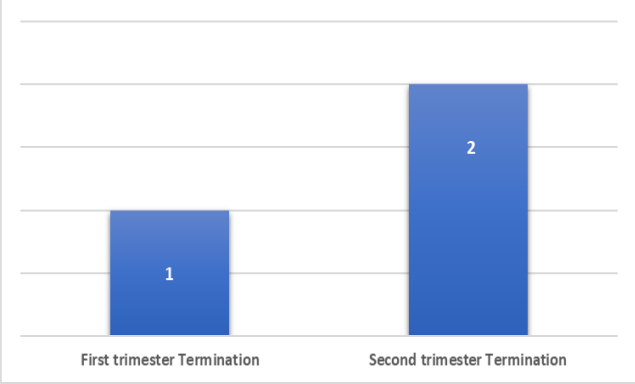

Figure 2. Termination of Pregnancy according to Trimester (n=3)

Table 2. Maternal Disease Progression during Pregnancy and Outcome with Acute Myeloid Leukemia over 5 years Review

Case	Rx during pregnancy			Adverse Event secondary to Rx	Pregnancy Outcome and MOD	Gestation week at Delivery /TOP	Postpartum Complications	Maternal Deaths
	Antenatal chemotherapy Regime	Gestation week of Initiation of Chemotherapy	Gestation week of Last Chemotherapy prior to delivery					
1	Indarubicin	25	No data	NIL	Full term; SVD	37	No data	No
2	Rx after delivery	N/A	N/A	N/A	Full term; CS	36	CS wound breakdowm	No
3	DA + HIDAC	24	31	Neutropenic sepsis	Preterm; CS	33	NIL	No
4	DA	24	34	Neutropenic sepsis	Full term; SVD	37	NIL	No
5	Rx after delivery	N/A	N/A	N/A	TOP	22	NIL	Yes (Refractory disease)
***6**	Rx after delivery	N/A	N/A	N/A	TOP	7	N/A	Yes
***7**	Palliative	N/A	N/A	N/A	Maternal and fetal demise	20	N/A	Yes (Advanced disease)
8	DA	28	28	Neutropenic sepsis	Preterm; SVD	34	NIL	No
9	Pt demise before Rx	N/A	N/A	N/A	Maternal and fetal demise	17	N/A	Yes (Advanced disease)
10	N/A	N/A	N/A	N/A	Miscarriage	9	N/A	No
11	Rx after delivery	N/A	N/A	N/A	TOP	19	NIL	No
12	DA	24	33	Neutropenic sepsis	Preterm; SVD	34	NIL	No

Rx, treatment; DA, Cytarabine-Daunorubicin; HIDAC, high-dose Cytarabine; TOP, termination of pregnancy; N/A, not applicable; SVD, spontaneous vertex delivery; CS, caesarean section.
**Same patient.*

Table 3. Antenatal Chemotherapy for Patients with Acute Myeloid Leukemia and Neonatal Outcome over 5 years Review

Case	Rx during pregnancy	Gestation week at Delivery	Apgar Score at 5 minutes	Birth Weight (kg)	Congenital Abnormalities	Neonatal Complications	Neonatal Death (Death within 28 days of birth)
1	Yes	37	No data	No data	No data	No data	No data
3	Yes	33	9	1.60	ASD, PDA	Neutropenic sepsis with multiorgan failure	Yes
4	Yes	37	10	2.25	NIL	NIL	No
8	Yes	34	9	1.90	NIL	Prematurity, neonatal sepsis, NNJ secondary to ABO incompatibility	No
12	Yes	34	9	2.17	NIL	NNJ, TTN	No

Rx, treatment; N/A, not applicable; ASD, atrial septal defect; VSD, ventricle septal defect; NNJ, neonatal jaundice; TTN, transient tachypnoeic of newborn.

IV. DISCUSSION

This data series shows the demographic characteristics, diagnosis, and pregnancy outcome of 12 acute myeloid leukemia in pregnancy occurring in a single Haematological Unit between 2014 to 2018.

The presenting symptoms and clinical picture of AML in pregnancy is like that of the non-pregnant cohort [3]. Some of these symptoms are non-specific and mimic those which are commonly reported during pregnancy such as fatigue, shortness of breath, minor epistaxis, and alteration in periphery blood counts, such as anaemia and thrombocytopenia which contributes to delay in referral and diagnosis of the disease. Recurrent infections and bleeding should raise suspicion as it can reflect bone marrow failure [3][4].

Differential diagnosis to be considered in these situations include HELLP syndrome, thrombotic microangiopathy, and immune mediated cytopenia. Investigations required for correct differentials diagnosis include full blood film examination besides routine full blood count, iron studies, coagulation and haemolysis screening, liver function test and renal profile [3]. If a diagnosis of leukemia is suspected, the diagnostic approach is the same as the non-pregnant cohort which is marrow sample examination including morphology, immunophenotyping and cytogenetic analysis, and molecular studies whenever possible to allow accurate diagnosis and sub-typing of the disease [5][6].

The treatment of AML during pregnancy remains a challenge as therapeutic decision must take into consideration the immediate health of the mother as well as long term effect on infant health. This is a decision burden not carried by the haematologist alone but rather a multidisciplinary team involving haematologist, obstetrician, anaesthesiologist, and neonatologist [6].

Another dilemma in the management of AML in pregnancy is the initiation of chemotherapy in pregnancy. The benefit and risks must be weighed out and discussed together with the patient including likely progression of the disease and high mortality rate with delaying treatment. The potential risks of antenatal chemotherapy to the unborn fetus should also be discussed with the patient including risk of teratogenicity, in-utero growth restrictions as well as neutropenic sepsis of the newborn. Our data series shows an overall 73% survival rate of AML in pregnancy, of which 100% achieved post-induction remission upon initiation of chemotherapy during pregnancy. It shows that chemotherapy can be safely administered during second and third trimester with good overall maternal outcome and 100% live birth rates.

Nevertheless, high dose cytarabine should be used cautiously and avoid administering after 35 weeks gestation due to its potential transient myelosuppression in the fetus which can last 3-4 weeks, placing neonates at substantial risk of anemia and sepsis [7]. While this risk is low, it can have profound effect leading to complications during the early neonatal period. There is recommendation to monitor fetus for anemia both before and after chemotherapy. This can be done using middle cerebral artery peak systolic velocity (MCA PSV) doppler and delivery considered if measurement was above 1.5 MoM which is suggestive of moderate to severe fetal anemia [7][8]. We do recommend a weekly MCA doppler surveillance and increasing the frequency as needed to optimise timing of delivery, balancing the risks of in-utero fetal demise and complications of preterm birth.

Hypomethylating agents such as azacytidine and decitabine are not recommended especially during early pregnancy due to its teratogenic effects via interruption of DNA methylation. It must be highlighted that in view of prenatal genetic testing was declined by parents, genetic abnormality cannot be ruled out in our case series, however, early animal studies have shown significant teratogenicity effect with such chemo agents [9][10]. Thus, we do recommend a mid trimester anomaly scan for all patients undergoing antenatal chemotherapy and invasive genetic testing offered whenever feasible.

Nevertheless, chemotherapy should not be withheld nor delayed due to pregnancy as it may be associated with poor maternal outcome. Therefore, in certain situations, termination of pregnancy prior to chemotherapy may need to be considered in favour of maternal well-being and included in the discussion with the woman.

Complications of chemotherapy-exposed neonates in our data series included neonatal sepsis, respiratory distress, and neonatal death. Prematurity may be a contributing factor as these neonates were delivered between 33-34 weeks gestation. As compared to deliveries at term (37 weeks and above), no neonatal complications were reported. Thus, timing of delivery should be individualised, aiming delivery as close to term as possible without compromising maternal or fetal well-being. Vaginal delivery remains the recommended mode of delivery while caesarean section is reserved for obstetrics reasons. Timing of delivery is also crucial and should be timed in such that it does not coincide with the nadir period of the last chemotherapy received. This is to reduce the risk of infection in both mother and the baby around the time of delivery.

In cases of diagnosis made in advance gestational age, we propose to terminate the pregnancy when feasible and postpone chemotherapy until post-delivery after careful assessment of maternal overall health status. This will avoid fetal exposure to chemotherapy and its possible complications during neonatal period.

Although it is well recognised of its advantages and benefits, breastfeeding is not recommended while undergoing chemotherapy. Owing to the prolong persistence of the chemo-agent metabolites which is found in breast milk, women on chemotherapy should be advised to interrupt breastfeeding for at least 6 weeks after treatment [11].

Engagement of pre-pregnancy counselling is of paramount importance and referral to such clinic is advisable for all patients of child-bearing age group undergoing chemotherapy. This is to avoid unnecessary adverse outcomes to both mother and fetus such as highlighted in case 6 and 7 in our cases series which is of the same patient who ultimately died due to treatment delay and advanced disease. We strongly recommend a long-acting reversible contraception in these circumstances and permanent contraceptives methods for couples who have completed family.

V. CONCLUSIONS

From our case series, we conclude that the management of AML in pregnancy should be a joint effort of a multidisciplinary team involving hematologist, obstetrician, anesthesiologist, and neonatologist. Termination of pregnancy in the first trimester should be considered prior to initiation of chemotherapy in favor of maternal well-being. Chemotherapy can be safely initiated in the second and third trimester, avoiding organogenesis period, with a good pregnancy outcome as demonstrated in our case series. Women receiving antenatal chemotherapy should be offered an anomaly scan and genetic testing when necessary and feasible. Fetuses exposed to antenatal chemotherapy should ideally be monitored for their growth and anemia with MCA doppler.

Pre-pregnancy counselling service for contraception should be provided and long-acting reversible contraception made available to patients of child-bearing age on chemotherapy.

Our study has its limitations. Its retrospective design with missing data has impacted our results analysis. Due to the small sample size in our series, we were unable to do subgroups analysis or comparison. Thus, we see a need for a national registry for leukemia in pregnancy to further aid in data collection and analysis to formulate a sound management guideline tailored to our local community to improve survival rates for both mother and fetus.

CONSENT TO PARTICIPATE

Written informed consent was obtained from the patient for the anonymized information to be published in this article.

CONFLICT OF INTEREST

The authors declare that there is no conflict of interest regarding the publication of this paper.

ACKNOWLEDGEMENT

We would like to thank both staffs and medical officers from both the obstetrics and gynecology department and hematology department of Ampang Hospital for their kind assistance with data collection.

REFERENCES

[1] Zaidi, Alia, Liza-Marie Johnson, Christopher L. Church, Wendy C. Gomez-Garcia, Marcela I. Popescu, Judith F. Margolin, and Raul C. Ribeiro. "Management of concurrent pregnancy and acute lymphoblastic malignancy in teenaged patients: two illustrative cases and review of the literature." Journal of Adolescent and Young Adult Oncology 3, no. 4 (2014): 160-175.

[2] Charlotte, Maggen, Wolters Vera ERA, Cardonick Elyce, Monica Fumagalli, Michael J. Halaska, and Amant Frédéric. "Pregnancy and Cancer: the INCIP Project." Current Oncology Reports 22, no. 2 (2020)..

[3] Fracchiolla, Nicola Stefano, Mariarita Sciumè, Francesco Dambrosi, Francesca Guidotti, Manuela Wally Ossola, Giovanna Chidini, Umberto Gianelli, Daniela Merlo, and Agostino Cortelezzi. "Acute myeloid leukemia and pregnancy: clinical experience from a single center and a review of the literature." BMC cancer 17 (2017): 1-8.

[4] Thomas, Xavier. "Acute myeloid leukemia in the pregnant patient." European journal of haematology (2015).

[5] Farhadfar, Nosha, Sonia Cerquozzi, Michael R. Hessenauer, Mark R. Litzow, William J. Hogan, Louis Letendre, Mrinal M. Patnaik, Ayalew Tefferi, and Naseema Gangat. "Acute leukemia in pregnancy: a single institution experience with 23 patients." Leukemia & Lymphoma 58, no. 5 (2017): 1052-1060.

[6] Greenlund, Laura JS, Louis Letendre, and Ayalew Tefferi. "Acute leukemia during pregnancy: a single institutional experience with 17 cases." Leukemia & Lymphoma 41, no. 5-6 (2001): 571-577.

[7] Parrott, Jessica, and Marium Holland. "Undetected severe fetal myelosuppression following administration of high-dose cytarabine for acute myeloid leukemia: is more frequent surveillance necessary?." Case Reports in Obstetrics and Gynecology 2017 (2017).

[8] Nowik, Christina M., Alina S. Gerrie, and Jonathan Wong. "Conservative management of presumed fetal anemia secondary to maternal chemotherapy for acute myeloid leukemia." American Journal of Perinatology Reports 11, no. 04 (2021): e137-e141.

[9] Lee, Bee Sun, Jameela Sathar, and Tee Chuan Ong. "Teratogenic effect of decitabine in a pregnant patient with acute myeloid leukemia: a case report." Hematology, Transfusion and Cell Therapy 44 (2022): 429-432.

[10] Derissen, Ellen JB, Jos H. Beijnen, and Jan HM Schellens. "Concise drug review: azacitidine and decitabine." The oncologist 18, no. 5 (2013): 619-624.

[11] Codacci-Pisanelli, Giovanni, Richard J. Honeywell, Natalie Asselin, Giulia Bellettini, Godefridus J. Peters, Elisa Giovannetti, and Fedro A. Peccatori. "Breastfeeding during R-CHOP chemotherapy: please abstain!." European Journal of Cancer 119 (2019): 107-111.