Acute leukemia and lymphoma in pregnancy, a retrospective study from a tertiary center in Malaysia

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ABSTRACT

Introduction: Most evidence about the management of cancer and hematological malignancy in pregnancy are derived from retrospective observational studies with a small sample size. Availability of sufficiently large data has enabled evidence-based decision-making in this clinical dilemma.

Materials and Methods: Retrospective study looking into patients diagnosed with acute leukemia or lymphoma in pregnancy from 1st January 2014 to 1st January 2020 in Ampang General Hospital including newly or previously diagnosed and relapsed disease

Results: 37 cases of acute leukemia or lymphoma in pregnancy occurred in 34 patients. Majority of acute leukemia or lymphoma in pregnancy diagnosed in 1st trimester or in the setting of previously established or relapsed disease was therapeutically terminated. Thirteen pregnancies treated with antenatal chemotherapy resulted in livebirths except one stillbirth. More adverse obstetric outcomes are observed in pregnancies that did not receive antenatal chemotherapy, but association did not reach statistical significance. There was no significant difference in fetal outcome between cohort with and without antenatal chemotherapy. No treatment related mortality was observed in pregnancies with antenatal chemotherapy. Overall survival for newly diagnosed acute leukemia in pregnancy is significantly better with antenatal chemotherapy versus no antenatal chemotherapy.

Conclusion: Treatment with chemotherapy in 2nd trimester of pregnancy onwards appears to have tolerable risks with favorable obstetric and fetal outcome. Deferment of treatment for acute leukemia in pregnancy to after delivery may cause increased risk of maternal and fetal adverse outcome.

KEYWORDS:
Leukemia, lymphoma, pregnancy, antenatal chemotherapy

INTRODUCTION

Oversea registries show that cancer in pregnancy is rare, estimated to be 1 in 1000 pregnancies and is the second most common cause of maternal death after gestation-related vascular complications.[1-2] Solid tumours (breast and cervix) accounted for the majority of cancer in pregnancy followed by lymphoma and leukemia.[3]

Historically, most evidences about the management of cancer and hematological malignancy in pregnancy are derived from retrospective observational studies with a small sample size. For the past decade, we have witnessed increasing publications from multinational multicenter studies. International Network of Cancer, Infertility and Pregnancy (INCIP) is the largest known registry with contributions from 67 centers from 28 countries that combines both oncological and obstetric data of women with a cancer diagnosis during pregnancy. Lymphomas and leukemias were listed as the second and fourth most common malignancies in pregnancy respectively in the registry.[4-5]

Availability of sufficiently large data has enabled evidence-based recommendations to be made to guide health care workers and patients in decision-making in this clinical dilemma. Recent recommendations concur with management guidelines from the International consensus meeting of Prenatal Hematologic Malignancies in 2014.[5-7] Recognizing the challenges balancing the welfare of both mother and fetus-in-utero, treatment of hematological malignancies in pregnancy should not differ from non-pregnant in principle. A host of factors such as subtype of malignancy, gestational age, aggressiveness of disease and tumor burden, maternal wellbeing during diagnosis in addition to psycho-social aspect and future fertility prospect need to be addressed during the formulation of treatment.

There is no local registry about the incidence of hematological malignancies in pregnancy. Local publication of guidelines, case series and case reports about managing solid tumour in pregnancy (breast, cervix and lung) are available but not hematological malignancies. A significant knowledge gap still exists regarding incidence of hematological malignancy and outcome for both pregnant mother and pregnancy in our local setting.

Department of Hematology of Ampang Hospital is Malaysia's national referal center for hematology diseases. This is a pilot study in Ampang Hospital with the objective to contribute more data and knowledge regarding hematological malignancies namely leukemias and lymphomas in pregnancy in our local population.

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MATERIALS AND METHODS

Study Type and Design

This is a retrospective study looking into patients diagnosed with acute leukemia or lymphoma in pregnancy from 1st January 2014 to 1st January 2020 in Ampang General Hospital. Acute leukemia and lymphoma are as per definition by WHO Classification of Tumours of Hematopoeitic and lymphoid Tissues revised 4th edition 2017. Patients were identified from the registry of delivery, termination of pregnancy and chemotherapy in Ampang General Hospital. Patients diagnosed with acute leukemia or lymphoma during pregnancy, including newly diagnosed, previously diagnosed active or relapsed disease from 1st January 2014 to 1st January 2020 in Ampang General Hospital were recruited.

Important variables that were collected included age, parity, gestational age during diagnosis, types of leukemia or lymphoma, types of treatment offered, pregnancy and fetal outcome and long-term outcome of the patients.

This study was registered with the National Medical Research Register Malaysia, and ethical approval was obtained from the Medical Research and Ethics Committee, Ministry of Health Malaysia (NMRR-19-3980-51915)

Statistical Analysis

The data analyses were carried out using the SPSS version 22. Descriptive data were expressed as mean ± standard deviation (SD) unless otherwise stated. Kruskal-Wallis ANOVA was used for non-normally distributed data. Categorical data were analyzed using Chi-square or Fisher's exact test. A value of $p<0.05$ is considered statistically significant.

The Kaplan-Meier method was used to estimate median survival times, and the log-rank test at a 5% significance level was used to test the equality of survival between groups. All p-values were 2-sided and values ≤0.05 were considered statistically significant.

RESULTS

Sociodemographic and Antenatal Characteristic

A total 37 cases of acute leukemia or lymphoma in pregnancy occurred in 34 patients during the study period in Ampang General Hospital. Three patients had two consecutive pregnancies complicated with acute leukemia or lymphoma. Most of the patients were Malay (83.8%) with a median age of 26 years upon diagnosis. Pregnancy complicated with lymphoma is more common than that of acute leukemia. A significant number of patients (27%) had either established diagnosis of the disease before the current pregnancy, refractory or relapsed disease. Sociodemographic and antenatal characteristics of the study population are summarised in Table I.

Antenatal Management

Diagnosis of acute leukemia or lymphoma or pregnancy was made predominantly during 1st (32.4%) and 2nd trimester of gestation (35.1%). Four diagnosis of lymphoma were made postpartum as the diagnostic procedure was deferred but the mothers had symptoms during pregnancy. The majority of acute leukemia or lymphoma in pregnancy (75%) diagnosed in 1st trimester were therapeutically terminated (Figure 1). The commonest indication is to facilitate treatment for patients that had acute leukemia or lymphoma in early pregnancy. One therapeutic termination of pregnancy was indicated for serious fetal anomalies due to unintended chemotherapy exposure. Termination of pregnancy in the setting of previously established or relapsed disease was 77.8%.

13 (35.1%) pregnancies began antenatal chemotherapy while 15 (40.5%) had treatment or diagnostic investigation deferred. None had received any surgery or radiotherapy. Two pregnancies that were diagnosed with lymphoma in 1st trimester of gestation had treatment delayed to 2nd trimester.

Three patients (one acute myeloid leukemia and two lymphomas) had consecutive pregnancies with poor obstetrics outcome. One had consecutive termination of pregnancy (TOP), another had a TOP with subsequent pregnancy ended with both maternal and fetal demise. The third patient had preterm delivery at 33rd weeks of gestation complicated with neonatal death at day 18 of birth.

OBSTETRIC AND FETAL OUTCOME

For the processing of obstetric outcomes, pregnancies that were terminated were excluded from the analysis (Table II). Among the twenty-eight remaining pregnancies, thirteen (46.4%) received antenatal chemotherapy. These pregnancies resulted in livebirths except one stillbirth. This stillbirth was seen in a pregnancy that had unplanned pregnancy during treatment for Hodgkin lymphoma resulting in 1st trimester exposure to chemotherapy.

Among twenty-eight pregnancies that continued, more adverse obstetric outcomes are observed in pregnancies that did not receive antenatal chemotherapy including two miscarriages and four maternal demises, but the association was not statistically significant (p=0.08). One missed marriage in 2nd trimester of therapy-related AML in pregnancy without antenatal chemotherapy had fetus with congenital anomalies (diaphragmatic hernia, ventricular septal defect and cyclopia). The majority of maternal deaths were related to disease related complications (one spontaneous tumor lysis in Burkitt lymphoma and two venous thromboembolisms in acute myeloid leukemia and diffuse large B cell lymphoma respectively). These patients deteriorated shortly after diagnosis while awaiting decision for treatment. One maternal death occurred in a pregnancy complicated with relapsed AML and the patient opted for palliative care.

76.2% livebirths were born prematurely and there was no significance difference between pregnancies that receive antenatal chemotherapy and those did not (p=1.00). This finding corresponds to similarly high rate of iatrogenic delivery either by elective Caesarean section or induction of labour.

28.5% of livebirths were small for gestational age defined by weight below 10th centile in growth chart with 33.3% in the

Table I: Sociodemograpic and antenatal characteristics of 37 pregnancies complicated with acute leukemia or lymphoma

	All patients, n = 37, %	Acute Leukemia, n=15, %	Lymphoma, n=22, %	*p* value
Median age	26 (23.5-27.5)	27 (24-32)	26 (23-28)	0.683
Ethnicity				
Malay	31 (83.8)	11 (73.3)	20 (90.9)	NA
Chinese	2 (5.4)	1 (6.7)	1 (4.5)	
Indian	2 (5.4)	1 (6.7)	1 (4.5)	
East Malaysian	1 (2.7)	1 (6.7)	0 (0)	
Other nationality	1 (2.7)	1 (6.7)	0 (0)	
Disease subtype				
Ph+ ALL		1 (6.7)		NA
Ph- ALL		1 (6.7)		
T- ALL		1 (6.7)		
AML with t(15:17)		2 (13.2)		
AML with inv (16)		3 (20.0)		
AML, NOS		5 (33.3)		
MDS transformed AML		1 (6.7)		
Therapy related AML		1 (6.7)		
Hodgkin lymphoma			13 (59.1)	
Burkitt's lymphoma			1 (4.5)	
DLBCL			6 (27.3)	
PMBL			2 (9.1%)	
Primigravida	14 (37.8)	4 (26.7)	10 (44.5)	0.47
Newly diagnosed				
Yes	27 (73.0)	11 (73.3)	16 (72.7)	1.00
No				
Known disease	6 (16.2)	2 (13.3)	4 (18.1)	
Relapsed disease	3 (8.1)	2 (13.3)	1 (4.5)	
Refractory	1 (2.7)	0 (0)	1 (4.5)	
Diagnosis of pregnancy or disease				
1st trimester	12 (32.4)	5 (33.3)	7 (31.8)	NA
2nd trimester	13 (35.1)	8 (53.3)	5 (22.7)	
3rd trimester	8 (21.6)	2 (13.3)	6 (27.3)	
Postpartum	4 (10.8)	0 (0)	4 (18.2)	
Antenatal Management				
Chemotherapy	13 (35.1)	6 (40.0)	7 (31.8)	0.70
No chemotherapy	15 (40.5)	5 (33.3)	10 (45.5)	
Termination of pregnancy (TOP)	9 (24.3)	4 (26.7)	5 (22.7)	

AML, acute myeloid leukemia; ALL, acute lymphoblastic leukemia; inv, inversion; NOS, non-otherwise specififed; APML, acute promyelocytic leukemia; HL, Hodgkin lymphoma; DLBCL, diffuse large B cell lymphoma; Ph, Philadelphia chromosome; PMBL, primary mediastinal B cell lymphoma; TOP, termination of pregnancy

Table II: Obstetric and fetal outcome of 28 pregnancies that did not have therapeutic termination

	Chemotherapy (n=13), %	No chemotherapy (n=15), %	*p* value
Leukemia	6 (46.2)	5 (33.3)	0.70
Lymphoma	7 (53.8)	10 (66.7)	
Median gestational week at diagnosis	23	24* (4 diagnosed postpartum)	
Outcome			0.08
No livebirth			
Miscarriages	0 (0)	2 (13.3)	
Maternal demise	0 (0)	4 (26.7)	
Stillbirth	1 (7.7)	0 (0)	
Live birth	12 (92.3)	9 (60)	
	Chemotherapy with livebirths (n=12)	**No chemotherapy with livebirths (n=9)**	
Median gestational week at delivery	34	34	1.00
Delivery			
32-37 week	9 (75.0)	8 (88.9)	1.00
>37 week	3 (25.0)	1 (11.1)	
LSCS	6 (50)	8 (88.9)	
Vaginal delivery	6 (50)	1 (11.1)	0.16
Iatrogenic delivery	9 (75)	9 (100)	0.23
Mean Birthweight (kg)	2.02	2.07	0.67
Small for gestational age	4 (33.3)	2 (22.2)	1.00
Median Apgar score at 5 minute	9	10	0.02
NICU admission	10 (83.3)	7 (77.8)	0.57
28 days neonatal death	1 (8.3)	0 (0)	1.00
Congenital anomalies	1 (8.3)	1 (11.1)	1.00

LCSC, lower segment Caesarean section; NICU, neonatal intensive care unit

Table III: Detailed description of 14 pregnancies that were exposed to chemotherapy

	Diagnosis	Disease status	GW diagnosis	GW Chemotherapy	Treatment	GW of Last Treatment	GW Delivery	Delivery Method	Maternal Adverse events	Fetal Adverse events
1	AML inv (16)	New	19	20	DA 3+7, 2 HIDAC	31	37	Induced, vaginal	Neutropenic sepsis	None
2	MDS transformed AML	New	25	28	DA 3+7	28	34	Induced, vaginal	Neutropenic sepsis	Presumed sepsis, prematurity
3	AML (NOS)	On treatment	11	1st trimester	decitabine	1st trimester	19	TOP	None	Fetal anomalies
4	AML (NOS)	New	22	24	DA 3+7, HIDAC	31	33	EMLSCS for fetal distress	Neutropenic sepsis leading to preterm labour	Fetal neutropenia, congenial heart disease neonatal death
5	AML (NOS)	New	24	24	DA 3+7	24	34	Induced, vaginal	Neutropenic sepsis	TTN, prematurity
6	APML	New	25	25	ATRA + idarubicin	25	34	Induced, vaginal	Neutropenic sepsis	None
7	APML	New	36	3rd trimester	ATRA	36	36	EMLCSC	Wound breakdown	Prematurity
8	HL	New	10	15	4 ABVD	31	37	Induced, EMLSCS	Bleomcin lung toxicity	Pneumonia
9	HL	New	27	30	1 ABVD	32	34	ELLSCS	None	Prematurity
10	DLBCL	New	21	21	6 RCHOP	21	34	ELLSCS	None	Prematuriy, respiratory distress syndrome
11	DLBCL	New	23	24	2 RCHOP	33	37	EMLSCS	None	None
12	DLBCL	New	8	24	3 RCHOP	30	33	vaginal	Neutropenic sepsis leading to preterm delivery	Prematurit, respirarory distress syndrome
13	PMBL	New	31	31	1 CHOP	31	34	Induced, vaginal	None	Pneumonia
14	Grey zone lymphoma	On treatment	1st trimester	1st trimester	6 AVD	29	29	vaginal	Pre-eclampsoa	IUGR and stillbirth

AML, acute myeloid leukemia; inv, inversion; NOS, non-otherwise specified; APML, acute promyelocytic leukemia; HL, Hodgkin lymphoma; DLBCL, diffuse large B cell lymphoma; PMBL, primary mediastinal B cell lymphoma; GW, gestational week; DA 3+7, daunorubicin and arabinoside; HIDAC, high dose cytarabine. ATRA, all-trans retinoic aicd; ABVD, adriamycin, bleomycin, vinblastine, dacarbazine; AVD, Adriamycin, vinblastine, dacarbazine; RCHOP, rituximab, cyclophosphamide, vincristine, prednisolone; TOP, termination of pregnancy, EMLSCS, emergency lower segment Caesarean section; ELLSCS, elective lower segment Caesarean section; TTN, transient tachypnea of newborn; IUGR, intrauterine growth restrction

cohort of antenatal chemotherapy and 22.2% in the cohort without antenatal chemotherapy. Birthweight, median week of delivery, modality of delivery, frequency of small for gestational age and neonatal intensive care admission do not differ significantly between these two cohorts. Median Apgar score at 5 minutes was significantly higher in livebirths that did not receive antenatal chemotherapy (10) than livebirths that receive antenatal chemotherapy (9) (p=0.02). One neonatal death with congenital heart disease complicated with neutropenic sepsis was seen in pregnancy that received antenatal chemotherapy for Hodgkin lymphoma. Another livebirth without antenatal chemotherapy had complex cyanotic heart disease.

PREGNANCIES EXPOSED TO CHEMOTHERAPY

Table III details fourteen pregnancies (seven leukemias and seven lymphomas) that were exposed to antenatal chemotherapy. No treatment-related maternal mortality was seen. Unintended chemotherapy exposures in 1st trimester occurred in two unplanned pregnancies (case number 3 and 14) during treatment of acute myeloid leukemia and grey zone lymphoma respectively. Case number 3 is a case of FLT3 positive AML in remission who had unintended decitabine maintenance administration in 1st trimester. The pregnancy was therapeutically terminated due to serious fetal anomalies detected during the antenatal scan. After delivery, the fetus was found to have physical abnormalities that include holoprosencephaly, cleft lip and palate, mid facial deformity and polydactyly(8). Case number 14 with grey zone lymphoma who had unplanned pregnancy diagnosed during the course of treatment was unintentionally exposed to adriamycin, vinblastine and dacarbazine in 1st trimester. The pregnancy was however complicated with intrauterine growth restriction secondary to preeclampsia leading to stillbirth at 29th weeks of pregnancy.

The remaining twelve pregnancies had planned chemotherapy from 2nd trimester onwards with all resulted in live births. The chemotherapeutic agents exposed are myriad and seven pregnancies have received more than one cycle of chemotherapy before delivery. Three received monoclonal antibody rituximab and two received ATRA. All received combination chemotherapy except one who received single-agent ATRA. The commonest maternal adverse events were neutropenic sepsis which occurred in less than half (42.8%) of the pregnancies.

The most common neonatal adverse events were related to complications of prematurity, more commonly due to iatrogenic premature delivery. However, an event of

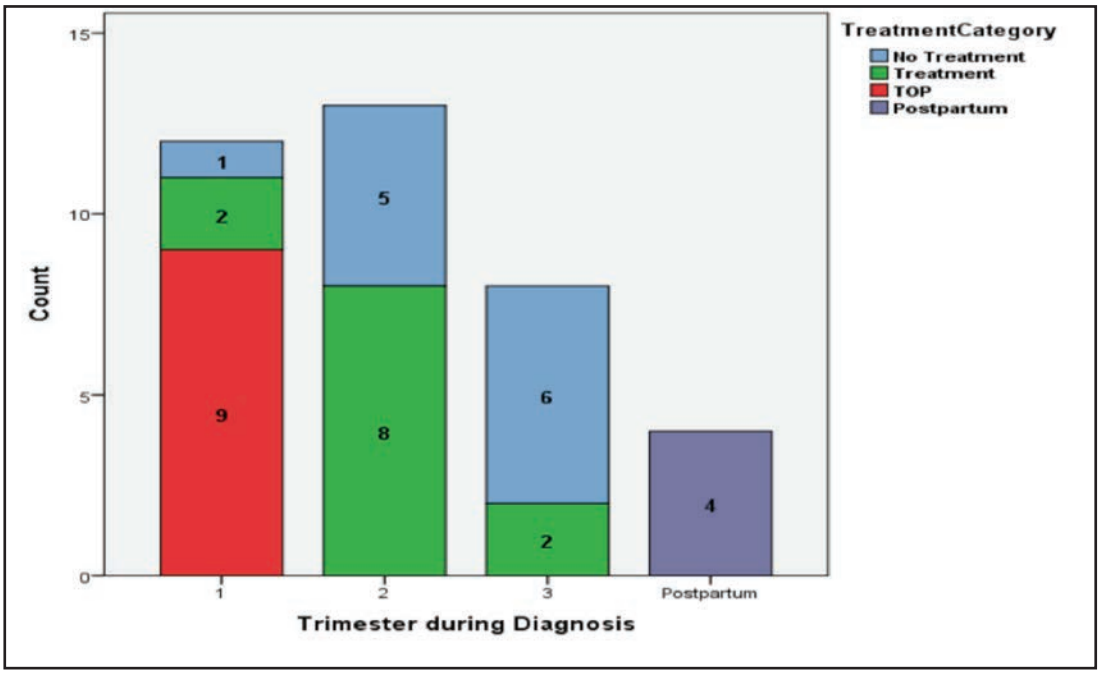

Fig. 1: Trimester when the diagnosis was made and antenatal management of 37 pregnancies complicated with acute leukemia or lymphoma

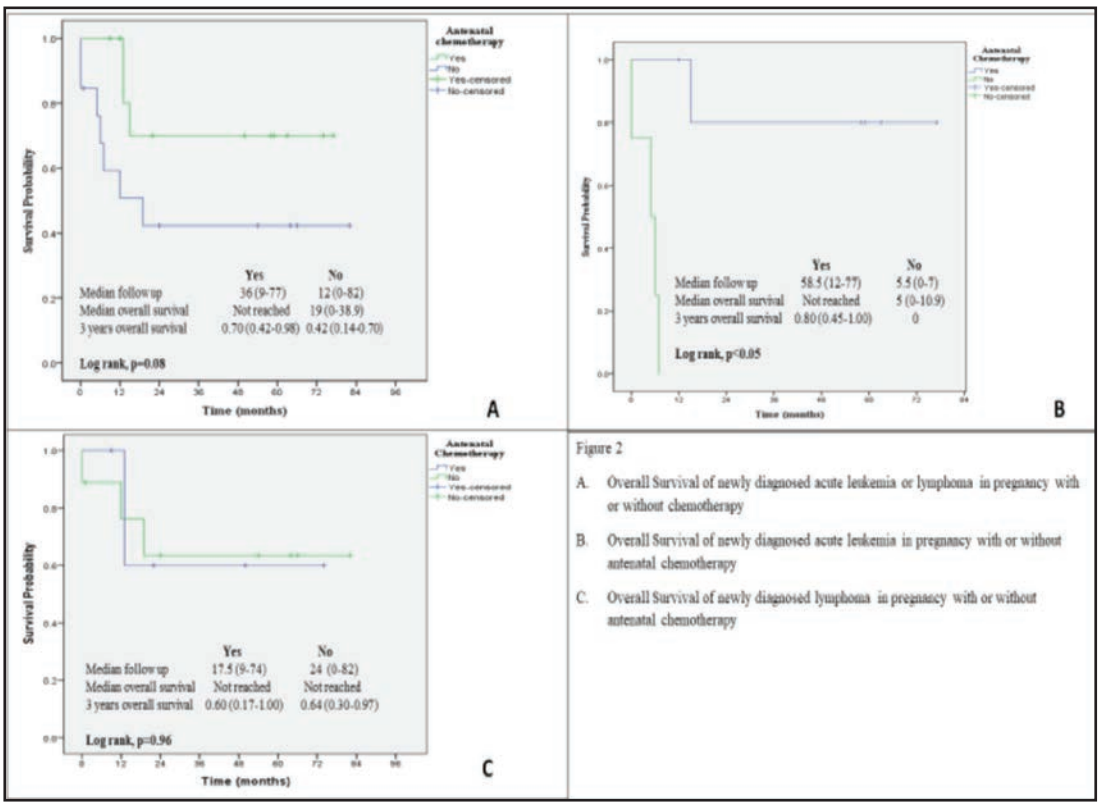

Fig. 2: Overall survival of newly diagnosed acute leukemia or lymphoma in pregnancy with or without chemotherapy

maternal neutropenic sepsis has resulted in preterm births leading to neonatal death at day 18 of life contributed by prematurity, neutropenic sepsis and congenital heart disease.

Maternal Long-term Outcome

Pregnancies with newly diagnosed acute leukemia or lymphoma that were not therapeutically terminated were selected for survival analysis. With median follow up of 19 months (0-82 months) of twenty-five pregnancies (Figure 2), antenatal chemotherapy has longer median survival (not reached) than cohort without antenatal chemotherapy, 19 months (95% CI, 0-38.9) but the difference is not significant (χ^2 (1), p=0.08). However, subgroup analysis of newly diagnosed acute leukemia in pregnancy shows that median survival is significantly better with antenatal chemotherapy versus no antenatal chemotherapy ($\chi^2(1)$, $p<0.05$), not reached as compared to 5 months. While subgroup analysis with newly diagnosed lymphoma in pregnancy does not demonstrate significant a difference of median survival with antenatal chemotherapy.

DISCUSSION

We observe significant premature livebirths due to iatrogenic delivery either by induction of labour or elective caesarean section in our study. The frequency is significantly higher compared to the frequency that occurred in the general population[9]. This finding is similar to many cohort studies and case series of cancers in pregnancy but the association between antenatal chemotherapy and preterm birth is controversial.[4,6,9-11] The frequency of preterm birth has no significant association with antenatal chemotherapy in our study. The decision for iatrogenic preterm birth may be multifactorial namely maternal deterioration, fetal distress, limitation of fetal exposure to chemotherapy, initiation of treatment, expediate diagnostic process or preference for planned controlled delivery. The question of whether iatrogenic preterm delivery should be a standard practice is controversial. Managing team needs to be aware that preterm delivery is known to have adverse effects on perinatal outcome and neurodevelopment later and Lu et al. have stated that preterm birth explained 89% of neonatal mortality in mother with cancers.[12] The effect of preterm births is also reflected in the increased incidence of neonatal intensive care admission of 81% of all livebirths.

Cytotoxic drugs used to treat acute leukemia and lymphoma such as cyclophosphamide, anthracyclines, cytarabine, vinca alkaloids are known to cross the placenta but probably with reduced fetal concentration with the placenta acting as barrier.[7] Administration of cytotoxic drugs during 1st trimester of pregnancy has been associated with embryo death, spontaneous abortion and teratogenicity with the estimated risk of 25% if combination chemotherapy.[6,13-14] Two pregnancies which had chemotherapy in 1st trimester had unfavorable outcome. Our cohort reported a likely association of unintended decitabine exposure in 1st trimester of pregnancy with serious fetal anomalies and was therapeutically aborted[8]. The other pregnancy was complicated with pre-eclampsia and stillbirth. The international consensus panel made the recommendations that termination of pregnancy may be contemplated if treatment cannot be delayed beyond 1st trimester due to maternal deteriorating condition or aggressiveness of disease.[6] At the time of writing, only one study has reported favorable outcome (no fetal anomaly, low rate of prematurity and favorable long term outcome) for pregnancy complicated with hematological malignancy that received chemotherapy in 1st trimester.[15] However, the majority of literatures have not reported similar finding.[16-17]

Antenatal chemotherapy from the 2nd trimester onwards is not associated with increased risk of congenital anomalies but with intrauterine growth restriction (IUGR), prematurity, lower birth weight, small for gestational age and a higher rate of stillbirth.[4,10.17-18] Our study reported no significant difference in frequency of congenital anomalies, small for gestational age and median birthweight between the cohort that received antenatal chemotherapy and the cohort that did not. Furthermore, 7 pregnancies in our cohort were treated with more than 1 cycle of chemotherapy with some receiving intensive chemotherapy such as high dose cytrabine with a favorable outcome. A study of breast cancer in pregnancy by Cardonick et al. shows that birthweight and rate of small for gestational age were not significantly affected by antenatal chemotherapy.[19] A retrospective study by Garofalo et al. from Italy also demonstrated that birthweight and rate of small for gestational age did not differ between the group that received chemotherapy and the group that did not.[20] The lack of difference may suggest that malignancy itself has adverse effects on fetal growth. Hematological malignancies probably has stronger association with small for gestational age compared with other solid tumors, while leukemia has a more profound effect than lymphoma.[10,12] The underlying mechanisms that have been proposed include having an impaired placental supply of oxygen and nutrient, maternal malnutrition, chronic inflammation, anemia and thrombosis.[20-21]

Transient neonatal myelosuppression (TNM), defined as leukopenia and/or neutropenia combined with aenmia and/or thrombocytopenia during the 1st week of life in newborns exposed to maternal chemotherapy during pregnancy has been reported in case reports and reviews. Neonates with TNM may be at risk of infection but the outcome was favorable with one death among fifteen cases of TNM from the review by Udink et al.[21] This complication is probably rare but the interval between antenatal chemotherapy to delivery probably is the most significant risk factor corresponding to maternal myelosuppression nadir.[21] In a case series of fifty neonates exposed to antenatal chemotherapy for acute leukemia in the last month of pregnancy, 33% were cytopenic at birth with one neonatal death at day 21 and additional mortality at day 90. We observed a neonatal death with antenatal exposure of high dose cytarabine consolidation two weeks before birth due to neutropenic sepsis complicated with multiple organ dysfunction and the absolute neutrophil count was 0 at birth coinciding with maternal neutropenic sepsis. Four neonates with antenatal chemotherapy (two had RCHOP, an ABVD and an ATRA) within three weeks of delivery did not suffer from such complication. Different regimes of chemotherapy with variable intensity leading to variable duration of myelosuppression may explain this observation. Therefore, it is recommended to avoid delivery during maternal myelosuppression nadir and antenatal chemotherapy should

not be administered beyond 35th weeks of gestation or within three weeks of anticipated delivery.[18,22]

Though antenatal chemotherapy poses significant risks to fetus and neonate, the neonatal outcome is generally favorable. As acute leukemia and certain lymphoma are generally aggressive diseases and patients may present with life threatening presentation, maternal well-being should take precedence and treatment should not be delayed and pregnant patient should be treated similarly as non-pregnant patient if possible. Delay in treatment due to concern for fetal risk may jeopardize maternal safety leading to maternal death during pregnancy. The largest registry of cancer in pregnancy did not report any chemotherapy- related mortality of all cancer types.[4] A multicenter retrospective study on lymphoma occurring in pregnancy did not observe any chemotherapy-related death but a retrospective study of 37 cases of acute leukemia in pregnancy reported an induction death.[23-24] Our data demonstrated the tolerability of antenatal chemotherapy for mothers with no treatment related mortality and the commonest toxicity being neutropenic sepsis which was manageable with good supportive treatment. The four early maternal deaths during pregnancy in our cohort without antenatal chemotherapy stresses that deferment of treatment for aggressive hematological malignancy to after delivery due to concern for fetal wellbeing may subject both mother and fetus to unacceptable risk of mortality and morbidity.

Our finding shows delay in treatment for acute leukemia in pregnancy may result in inferior overall survival probably due to early mortality. Lack of significant difference of overall survival of lymphoma in pregnancy based on receival of antenatal chemotherapy indicates selected patients with indolent course, low tumor burden, diagnosis at advanced pregnancy may have treatment deferred to after delivery after careful assessment without affecting the long term outcome.[7,24-25]

We observe significant pregnancies in our cohort which were complicated with non-newly diagnosed leukemia or lymphoma have a higher incidence of therapeutic pregnancy termination and poorer obstetric outcome. Furthermore, 3 mothers had 2 consecutive pregnancies complicated with active hematological malignancies implies a lack of integration of fertility planning and contraceptive counselling into the management of female patients with hematological malignancies in reproductive age. Female cancer patients within reproductive age may remain fertile with normal menstruation after chemotherapy or radiotherapy and 45% participants of one cross-sectional study would terminate the pregnancy if they became pregnant during treatment. In addition to that, a majority of participants did not practice effective contraception method during cancer treatment.[26] Pregnancy should be avoided within 2-3 years of remission of hematological malignancies due to probability of recurrence during this period.[1] Unplanned pregnancy during or shortly after cancer treatment may result in unintended chemotherapy administration which is demonstrated in two cases in our cohort resulting in poor obstetric and neonatal outcome.

Most of the retrospective and observational studies are derived from European countries and our study offers a perspective from Malaysia, a developing country in South East Asia. It offers an insight into our treatment strategy and challenges faced in managing pregnancy associated with acute leukemia or lymphoma in comparison with other countries.

One significant limitation is the small sample size from a single center and with retrospective research design. Multicenter involvement with the establishment of a national registry for hematological malignancy in pregnancy in the future would allow collaboration with the international registry to improve clinical knowledge and recommend evidence-based practice. In addition to that, a larger sample size may allow analysis into specific hematological malignancy to enable disease-specific management recommendations.

CONCLUSION

Management of acute leukemia or lymphoma in pregnancy is challenging. Treatment with chemotherapy in 2nd trimester of pregnancy onwards appears to have tolerable risks with favorable obstetric and fetal outcome. Deferment of treatment for acute leukemia in pregnancy to after delivery may cause increased risk of maternal and fetal adverse outcome but may be considered in certain subsets of lymphoma in pregnancy.

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DECLARATIONS

This study was approved by the medical research and ethics committee, Ministry of Health Malaysia NMRR-19-3980-51915.

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