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Management of acute promyelocytic Leukaemia: A systematic study and meta-analysis

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ABSTRACT

A rare but severe variant of Acute Myeloid Leukemia (AML) known as Acute Promyelocytic Leukemia (APL) needs prompt medical attention. When APL is discovered during pregnancy, treatment options must be carefully assessed against any dangers to the growing fetus. This complicates APL management. To determine the effectiveness and safety of various treatment methods, a thorough study and meta-analysis of the therapy of APL during pregnancy was carried out. A comprehensive search of digital databases for papers released during 2000-2020 was part of the investigation. Once relevant articles had been located, they were further screened, and duplicates were removed. Moreover, 120 pregnant women confirmed to have APL were included in 78 studies that satisfied the criteria. Regardless of the induction method or gestational age, a complete remission frequency is 91%. Women in the first trimester had more excellent rates of spontaneous and induced abortion. The statistical analysis was performed using the SPSS software. There were just four stillbirths among third-trimester women. Respiratory distress syndrome affected 12 of the 16 new-borns with neonatal problems, but most of them (apart from 2 premature deaths) did well. According to this research's results, gestational age has little bearing on the mother's outcomes but is directly tied to fetal survivability. Our findings might help decide on a treatment that involves the individual being treated, a haematologist, a doctor who treats pregnant women, and a neonatologist.

Keywords: Acute Promyelocytic Leukemia (APL), pregnancy, management, complete remission frequency, chemotherapy

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INTRODUCTION

A rare but deadly type of blood cancer that can develop during pregnancy is known as Acute Promyelocytic Leukemia (APL). Promyelocytes, which are immature white blood cells, exhibit aberrant proliferation and accumulation occurred among blood and bone marrow, which are characteristics in the condition. Quick and aggressive treatment is necessary to avoid fatal consequences and significant complications from APL. However, managing APL throughout the pregnancy may be especially difficult since it's crucial to consider the benefits and dangers of therapy for the woman and the fetus [1]. APL is thought to occur in about 1 in every 75,000 pregnancies during pregnancy. It frequently manifests during phase II or III phase and can result in several symptoms, including exhaustion, bleeding, fever, and shortness of breath. Clinical examination, blood tests, bone marrow biopsy, and genetic testing confirm an APL diagnosis [2]. Hematologists, obstetricians, neonatologists, and other medical professionals must collaborate to treat APL during pregnancy because the condition is complicated. The mainstay of therapies for APL is chemotherapy, which frequently combines Arsenic Trioxide (ATO) and All-Trans Retinoic Acid (ATRA). But using cancer treatment while pregnant obtained a number of risks in the developing fetus, such as congenital abnormalities, growth retardation, and fetal loss [3].

The decision to begin chemotherapy while pregnant requires considering the severity of APL, the pregnancy stage, and the therapy's hazards and benefits. ATRA alone, which carries a lower risk of fetal toxicity, can be used to start treatment in some circumstances or postponed until after delivery. Delaying medical care, however, might also make it more likely that the sickness will spread and cause issues for the mother [4]. Supportive treatment procedures, including blood transfusions, antibiotics, and anticoagulation therapy, can be required in addition to chemotherapy to treat APL consequences like bleeding and infection. Close maternal and fetal status monitoring is crucial throughout treatment, including routine fetal ultrasound and non-invasive prenatal testing for chromosomal abnormalities [5].

To examine the medical results recorded for both the mother and the baby in various situations; this study aims to perform a thorough systematic research analysis. A particular focus will be placed on the usage of contemporary treatments based on the baby's gestational age.

Relate works

The development of APL therapy emphasizes significant turning points that resulted in the current standard-of-care APL therapy in [6]. They talk about management strategies and therapeutic protocols to reduce initiation mortality. Includes comprehensive suggestions for detecting and treating the most significant side effects, including those related to ATRA and ATO toxicity, Blood vessel disease QT the extension, APL development condition, along with additional toxicity [7]. It was shown that the schedule devoid of chemotherapeutic alongside ATO/ATRA is highly effective in treating de novo APL. It is currently the standard treatment for young people with a safe illness. APL women still frequently die suddenly, especially those more mature, highlighting the importance of early diagnosis, assistance, and rapid availability of ATRA-based therapy [8]. The leukemogenesis, treatment, and resistance mechanisms were examined by [9]. To get to a resolution on suggestions based on the most accurate available information and our clinical expertise, they researched the pertinent literature. They employed the Delphi technique among the co-authors [10]. The development of oral arsenic RIF as a therapeutic option for APL, emphasizing how to manage any issues that may arise throughout initiation therapy [11]. They discuss coagulopathy, premature death, and the unique challenges of care for people with high-risk APL and those who have relapsed APL. They also make recommendations and point out current programs that try to improve the results for women with high-risk and retreated APL as well as the persistently elevated early mortality rate [12]. APL's six-decade development is examined in which begins with the treatment's initial description and concludes with chemotherapy-free ATRA-ATO therapy [13]. Three clinical trials were carried out to investigate the long-term results of women treated for recently found APL, utilizing ATRA and ATO, with or without GO. Low-risk women with leukocytosis got GO on day 1, whereas high-risk women had a white blood cell count more than 10 109/L [14]. The genetic landscape of variant APL, their role in its development, and clinical insights into its management were all examined in the [15]. The authors recommend that RNA sequencers and DNA screening be used to make the diagnosis as soon as feasible.

METHODS

Search technique and study selection

Utilizing predefined criteria for searching, a systematic evaluation of research from the start to January 2020 was conducted in accordance with the PRISMA guidelines using the databases of Web of Science, PubMed, and Scopus. The most important words are "acute promyelocytic leukaemia," "acute myeloid leukaemia," "acute leukaemia," "haematologic malignancy," and "pregnancy," along with "pregnant" was used, but only for publications. Those, at a minimum, provide a detailed summary written in English. Once suitable articles had been found, they underwent additional screening, and duplicates were eliminated. Finally, 78 articles with 120 pregnant women who had been diagnosed with APL met the eligibility requirements. The procedure diagram for choosing a study is shown in figure 1.

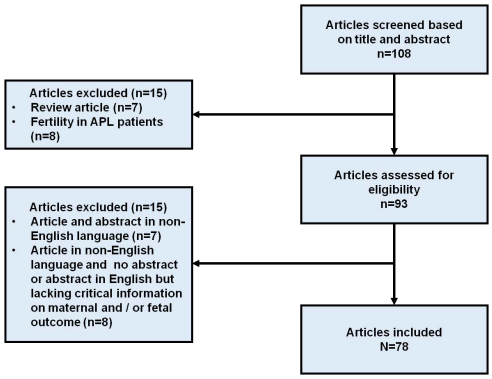

Fig. 1. Schematic view of choosing a study

Extraction of data

The data that follows was taken from the chosen studies: gestational age at delivery and diagnosis, new-born status at birth, type of delivery/abortion, such as any obstetric or complications, Apgar scores and weight, general medical condition of the mother and new-born, and length of afterward at the point of the study's conclusion.

Statistical analysis

In a single-variant, the student t-test was used to evaluate continuous portions while chi-squared or Fischer's exact evaluations were used to examine divisions. For each and every symmetrical p-value, the significance threshold was set at 0.06.

RESULTS AND DISCUSSION

The research comprised 120 pregnant mothers who had been given an APL diagnosis. The majority of cases (n=22) were presented as single case reports, with the exception of one series of 16 women and a few papers with 2-4 individuals (Table 1).

Tab. 1. The study includes reports of cases of APL during pregnant

Articles in Number	Women's Number	Women reported by Article in Number
22 [16-42]	22	1
4 [43-46]	8	2
4 [47-50]	12	3
1 [51]	4	4
1 [52]	74	>4

Pregnant women were, on average, 32 years old (range: 18 years-45 years) at the time of APL diagnosis. An average maternity period of 6 months (encompassing of 1 to 10 months of duration) was used to diagnose APL. The first, second, and third APLs were found. Women aged 20 years, 65 years, and 25 years had 3-months intervals, severally, as well as in 6 additional cases just after birth. 4 patients' age at delivery was unclear.

A summary of the presenting features is shown in table 2, which also includes the platelet counts, blood and White Blood Cell (WBC) levels, genetic diagnosis, relapse-risk score, and coagulopathy. When APL was diagnosed, the average platelet counts and WBC has obtained at 1.9 110/L (assortment, 0.5-296) and 23 $\times 10^9$/L (assortment, 1.6-132), correspondingly. 50 women (85%) had thrombocytopenia less than 41 109/L, while 9 women (15%) had hyperleukocytosis greater than 11 $\times$ 10^9 /L. In 37 individuals (89%), blood sugar levels less than 10 g/dL were indicative of anaemia. Of the 57 women for whom this information was accessible, women were categorized as low-, intermediate-, and high-risk in 10 (14%), 39 (73%), and 9 (13%) of the cases, correspondingly. 44 of the 54 women's (or 82% of them) had coagulopathy at the time of their initial visit. Among the 90 individuals for whom this information was available, 69 women (or 77%) had a diagnosis of genetics recorded. Central nervous system damage was absent in any case.

Pregnancy results

The remaining 120 pregnant women were deemed competent for initiation counselling with the exception of 6 who were hospitalized in profoundly poor clinical circumstances and were unable to receive therapy (Table 2). The majority of women (32; 31%) or those paired with chemotherapy (35; 34%) underwent induction treatment with ATRA, while another 14 women (8%) got chemotherapy that was based on anthracyclines. 15 of the latter had received treatment between 1973 and 1995, when ATRA was not yet commercially accessible, and the remaining 5 women had chemotherapy-only care between 1995 and 2002 at the doctor's

Tab. 2. Women with APL that appears during pregnancy tend to have specific features

Features	No. (%)	Average (Range)
Age of pregnancy at diagnosis (n-116)		24 (1-41)
1st Three-month periods	20 (16)	
2nd Three-month periods	65 (49)	
3rd Three-month periods	25 (30)	
After Pregnancy	6 (5)	
Year, Age		32 (18-45)
(15 Years-19 Years)	6 (7)	
(20 Years-29 Years)	51 (45)	
(30 Years-39 Years)	49 (44)	
-40 Years	14 (4)	
count of platelets, × 109 /L (n =60)		23 (1.6-132)
< 30 or	50 (85)	
30 or 30 >	10 (15)	
Count of WBC, × 109 /L (n=60)		1.9 (0.5-296)
<10	48 (76)	
10-40	5 (10)	
40-60	4 (6)	
60 or >	3 (8)	
Danger Scale (n=58)		
High	9 (13)	
Low	10 (14)	-
Intermediate	39 (73)	
Hemoglobin, g/dL (n=42)		8.4 (3.3-13)
<20	37 (89)	
20 or 20 >	5 (11)	
Testing for genetics (n=92)		
Yes	23 (25)	-
No	69 (75)	
Coagulopathy (n=55)		
Yes	11 (18)	-
No	44 (82)	

discretion. 3 women were subsequently served (2016-2019) with an ATO-based protocol following a miscarriage at 26 weeks of pregnancy or the birth of normal babies at 35 weeks and 39 weeks. 10 women's died during induction therapy, leaving 88 women who might have been evaluated for response with a response rate of 78 (89%), achieving Complete Remission (CR). 3 cerebral hemorrhages, 3 multi-organ failures, and one infection were the causes of death in 7 individuals. One patient who was refused blood products experienced an ischemic stroke, and the extreme differentiating disease was a factor in the breakdown of 2 multi-organ systems. After each diagnosis, each person passed away. Table 3 demonstrates that neither the kind of induction procedure utilized nor the gestational age had a statistically important effect on the CR rate.

Tab. 3. Therapy for initiation and outcomes

Therapy Initiation		Only using Chemotherapy	Only using ATRA	ATRA + Ida/Dauno	Chemotherapy + ATRA	Chemotherapy ± ATO ± ATRA
No. of Women's (n=114)		27 (23)	32(31)	35 (34)	14 (8)	6 (4)
CR/No. of women's	1st trimester (27/27)	8/8 (100)	5/5 (100)	7/7 (100)	6/6 (100)	-
	2nd trimester (41/48)	10/12 (88)	7/11 (71)	14/15 (94)	7/8 (93)	3/3 (100)
	3rd trimester (31/35)	4/5 (79)	13/14 (96)	13/13 (100)	-	2/3 (97)
	Total (99/110)	22/25 (91)	25/30 (92)	34/35 (98)	13/14(96)	5/6 (91)

Fetal results

Table 4 lists the results of pregnancies. 42 pregnancies overall resulted in impulsive abortion (9; 27%), caused abortion (17; 37%), an early miscarriage (3; 25%), or death of the mother while pregnant (3; 4%). 15 of 17 pregnancies among women with APL who were identified during the I phrase of the gestational periods (89%) reflected in abortions, among 9 of those caused during pregnancy life spans of 10 weeks (extend, 4-12) and 5 occurring spontaneously at a gestational age of 8 weeks (extend, 5–10). The residual 2 women carried their pregnancies till they gave birth to healthy babies through caesarean delivery at 33 weeks or vaginally at 38 weeks.

Tab. 4. Results of pregnancies by age at conception

Results of Pregnancies		Childbirth (n=78)			Induced Miscarriage (n=42)			
		Caesarean	Vaginal	Unknown	Spontaneous	Therapeutic	Late still Birth	Maternal Death during Pregnancy
Overall		42 (59)	31 (38)	5 (3)	9 (27)	17 (37)	13 (25)	3 (11)
1st trimester	No. of women's (%)	3 (75)	2 (25)	-	8 (38)	11 (62)	-	-
	Age of Pregnancy at Recognition, weeks	5	9	-	8 (5-10)	10 (4-12)	-	-
	Age at Birth in Pregnancy, weeks	34	41	-	8 (7-13)	10 (6-19)	-	-
2nd trimester	No. of women's (%)	21 (58)	16 (40)	1 (2)	3 (15)	4 (22)	8 (51)	2 (12)
	Age of Pregnancy at Recognition, weeks	25 (12-29)	24 (12-29)	-	15,20	14 (14-15)	27 (24-29)	26,29
	Age at Birth in Pregnancy, weeks	33 (24-39)	34 (25-36)	-	20,20	16 (14-18)	27 (26-31)	26,29
3rd trimester	No. of women's (%)	19 (57)	15 (41)	1 (2)	-	-	4 (60)	2 (40)
	Age of Pregnancy at Recognition, weeks	34 (28-37)	39 (28-41)	-	-	-	30	30
	Age at Birth in Pregnancy, weeks	32 (31-38)	37 (28-41)	-	-	-	30	30

15 of the 47 women (31%) who experienced pregnancies ending in stillbirth, induced abortion, miscarriage, or maternal death without delivery did so in the II phrase. In III phrase diagnosed women, 3 of 34 pregnancies (7%) resulted in maternal mortality or miscarriage while pregnant. The remaining 32 women underwent a cesarean delivery (n=18), a vaginal birth (n=14), an unknown method (n=2), or were not diagnosed until the 3rd trimester (n=28) or shortly after delivery (n=5). When given an APL diagnosis in the 1st trimester, women were more likely to have an unplanned or forced abortion (89% *vs.* 31%; p<0.0002) than when given an APL diagnosis in the second trimester. Gestational women have APL identified in the 3rd trimester gave birth to significantly more children compared with those detected in the I or II phrase (p<0.0002). 16 babies were delivered at term (36 weeks or more gestation), while 46 babies were born preterm (between 29 weeks and 37 weeks). Infants delivered before 37 weeks of pregnancy and at term had median birth weights of 2211 g (interquartile range) and 3135 (interquartile range), respectively. At 1 and 5 minutes, the median Apgar scores were 6 (interquartile range) and 16, respectively. In 17 out of 66 neonates (26%) who were all preterm and had a median pregnancy age of 33 weeks and weight of 1999 g, there were reports of perinatal problems. There were 12 new-borns that had respiratory distress syndrome. Furthermore, 4 of the patients had cerebral haemorrhage, patent ductus arteriosus, pulmonary hypoplasia, blocked atrial premature contractions and arrhythmia, bilateral hydronephrosis in a single instance, and cerebral haemorrhage. Every new born showed great outcomes, with the exception of one kid with respiratory distress syndrome who passed away from a pulmonary haemorrhage 30 minutes after delivery, one infant with Potter's syndrome who continued to use nasal oxygen and diuretics, and one infant whose general development was poor growth was still being monitored at the time of publishing. The kids with problems at delivery were 8/24, 3/14, and 7/24, respectively, based on whether the APL women had received ATRA alone, chemotherapy alone, or ATRA + chemotherapy for initiation treatment. But there were no significant statistical changes. Neonatal issues varied depending on the stage of pregnancy at evaluation, with 2/3 happening in the initial trimester, 12/33 in the following one, and 4/28 in the final trimester; however, once more, these changes were not statistically significant. Additionally, neither age nor any present traits affected the chance of neonatal issues. To identify connections between miscarriages, still-births and the kind of initiation therapy were illustrated in the tables 5 and 6.

Tab. 5. New-borns' birth weight and Apgar scores according to gestational age at diagnosis

Trimester of Pregnancy			1st Trimester	2nd Trimester	3rd Trimester	Overall
Weight at birth, g	Preterm	N	8	31	13	52
		Median	1831	1986	2056	2211
	At term	N	4	0	7	11
		Median	3061	-	3135	3135
Apgar Score	1 min	N	0	16	18	34
		Median	-	7	9	7
	5 min	N	0	19	13	32
		Median	-	8	9	10

Tab. 6. Miscarriage and induction therapy: A connection

Therapy Initiation		Only using Chemotherapy	Only using ATRA	ATRA + Ida/ Dauno	Chemotherapy + ATRA	Chemotherapy ± ATO ± ATRA
No. of Women who Achieved CR (n=99)		**22**	**25**	**34**	**13**	**5**
Miscarriage	1st trimester (7/0)	2/0	-	3/0	3/0	-
	2nd trimester (0/5)	-	0/2	0/3	-	0/2
	3rd trimester (0/3)	0/1	0/2	-	-	-
	Total (7/8)	02-Jan	0/4	03-Mar	3/0	0/2

CONCLUSION

This work constitutes the most comprehensive overview of the literature to date on the topic, including insightful management recommendations for situations involving APL-diagnosed pregnant patients. In reality, there is still a good chance of obtaining Complete Remission (CR) and eventually a cure; in fact, it's probably not much less than for women who are not pregnant. However, there is a statistically significant rise in the abortion rate in early pregnancy, which is highly correlated with gestational age in terms of fetal prognosis. Low birth weight and prematurity were very common, with the most common fetal outcome in premature new-borns being syndrome of breathing problems. Although there haven't been any teratogenic consequences in new-borns documented, ATO, chemotherapy, and other possibly teratogenic drugs should be used with caution and in line with the age of pregnancy. Incorporating the individual in question, obstetricians, neonatologist, and hematologist into the process of making choices proves essential when evaluating these ideas.

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