Management of the pregnant patient with acute promyelocytic leukemia (APL) is a challenge. Immediate treatment of APL is critical, as it is an oncologic emergency, with a high risk of morbidity and mortality associated with disseminated intravascular coagulation. However, administration of chemotherapy and differentiating agents in pregnancy is controversial because of potential teratogenic effects. In addition, complications associated with APL, including retinoic acid syndrome, add to the complexity of management. To better understand how to manage this complex patient care situation, we searched the PubMed database (January 1972–May 2008) for English-language articles about maternal and fetal outcomes resulting from APL treatment during pregnancy. A total of 42 cases from 35 articles were identified: 12 first-trimester, 21 second-trimester, and 9 third-trimester cases. The most commonly administered agents were all-trans-retinoic acid (ATRA), anthracyclines, and antimetabolites. Complete remission was reported in 35 (83%) of 42 patients. Administration of ATRA or chemotherapy in the first trimester was associated with an increased risk of fetal malformations and spontaneous abortion, whereas administration in the second and third trimesters was associated with relatively favorable fetal outcomes. The overall treatment of the pregnant patient with APL should include a discussion about pregnancy termination, especially if APL is diagnosed in the first trimester. If the pregnancy is to continue, then the appropriate chemotherapy regimen needs to be determined. Frequent fetal monitoring, along with aggressive management of potential APL-related complications, is necessary to allow for optimal maternal and fetal outcomes.

**Key Words:** acute promyelocytic leukemia, APL, pregnancy, treatment, hematology.

*(Pharmcotherapy 2009;29(6):709–724)*
Management of acute leukemia during pregnancy is quite challenging for the clinician, as well as for the patient and her family. If the diagnosis is acute promyelocytic leukemia (APL), a subtype of acute myeloid leukemia, then this challenge is even greater. Because APL is considered an oncologic emergency, it should be treated promptly to avoid the bleeding complications and mortality associated with disseminated intravascular coagulation (DIC). With a pregnant patient, however, the well-being of both the patient and fetus must be considered. An obvious caveat of administering chemotherapy to a pregnant patient is the potential for fetal malformations and spontaneous abortion. As to the maternal-fetal conflict, if the patient elects to continue the pregnancy while receiving APL treatment, the potential exists for adverse fetal outcomes; however, if the patient decides to delay APL treatment for the sake of the fetus, then there is a high risk of maternal mortality. Nonetheless, the overall management of both APL and pregnancy (i.e., whether to continue or terminate the pregnancy) should be determined immediately after receiving the leukemia diagnosis.

Leukemia affects approximately 1 in 75,000 pregnancies; the exact incidence of APL in pregnancy has not been reported in the literature. Although the diagnosis of APL during pregnancy is rare, there are numerous case reports in the literature to warrant a review in order to guide clinicians in managing this complex patient care situation. To our knowledge, a comprehensive review of these cases has not been published. Thus, we performed a literature search of the PubMed database using the search terms acute promyelocytic leukemia and pregnancy to review both maternal and fetal outcomes resulting from treatment of APL during pregnancy. All relevant English-language articles published between January 1972 and May 2008 were included. Additional case reports, selected from the references of the PubMed-search articles, were also included. Table 1 provides a summary of the case reports and letters that were selected for this review.

Acute Promyelocytic Leukemia

The incidence of acute myeloid leukemia in the general population is 2.7/100,000 individuals, with APL accounting for 5–15% of these cases. Among all the acute myeloid leukemia subtypes, APL has the distinction of being the most curable. The median age at diagnosis is 40 years, which is younger than with the other acute myeloid leukemia subtypes. The fact that APL is more common in younger patients increases the possibility that it may occur during pregnancy.

In APL, a differentiation and maturation arrest occurs in the myeloid lineage, resulting in an accumulation of promyelocytes in the bone marrow and peripheral blood. The cytogenetic abnormality translocation (15;17), which is present in most APL cases, leads to the fusion of the retinoic acid receptor alpha (RARα) gene, located on chromosome 17, with the promyelocytic leukemia (PML) gene, located on chromosome 15. This results in the PML-RARα fusion protein, which blocks differentiation, leading to uncontrolled proliferation of promyelocytes.

Since APL is considered to be an oncologic emergency, proper immediate treatment for the patient is critical. Treatment is generally started immediately if there is suspicion of APL, without waiting for a confirmatory genetic diagnosis. Cytogenetic analysis is still essential for diagnosis but should not delay therapy due to significant improvements in coagulopathy shortly after treatment initiation with all-trans-retinoic acid (ATRA). Phases of Treatment

Generally, the treatment of acute leukemia consists of three phases: induction, consolidation, and maintenance. Selected chemotherapy regimens for APL are outlined in Table 2. The overall goal of treatment is to induce and maintain a morphologic complete remission, which is defined as a morphologic leukemia-free condition (< 5% bone marrow blasts) with absolute neutrophil count of at least 1 x 10^3/mm³ and platelet count of at least 100 x 10^3/mm³. To assess response, a bone marrow biopsy is typically performed 4–6 weeks after the start of treatment. Recently, maintaining a complete molecular remission has been established as another therapeutic goal in APL. Complete molecular remission is achieved when molecular studies are negative for the PML-RARα fusion transcript. Molecular response is assessed by reverse transcriptase polymerase chain reaction by using bone marrow or peripheral blood.
samples. This test is performed every 3 months for 2 years once the patient is in morphologic complete remission and has completed consolidation therapy.44

Induction

Current APL practice guidelines from the National Comprehensive Cancer Network state that induction therapy should consist of ATRA and an anthracycline (idarubicin or daunorubicin).44 This recommendation is based on the high rates of complete remission reported in both the Gruppo Italiano Malattie Ematologiche dell’Adulto (GIMEMA) 93 trial and the Programa para el Tratamiento de Hemopatías Malignas (PETHEMA) LPA 94 trial (95% and 89%, respectively).40, 44, 46 In contrast to sequential therapy (ATRA followed by chemotherapy), combination ATRA-anthracycline therapy was associated with a lower relapse rate at 2 years (combination 6% vs sequential 16%, p=0.04).44, 47 Approximately 70–80% of patients with a new diagnosis who are treated with ATRA and chemotherapy reach long-term remission and are considered to be cured.39

For patients who are unable to tolerate anthracyclines, a combination of ATRA and arsenic trioxide may be used. A complete remission rate of 96% was reported for patients who received this combination.41, 44 Cytarabine has also been added to daunorubicin and ATRA induction therapy. For high-risk patients (age > 60 yrs, white blood cell count > 10 x 10^3/mm^3), improved survival was noted with the cytarabine-containing regimen (2-yr survival 93% vs 79% without cytarabine).42, 44

Consolidation

Consolidation is typically started after morphologic complete remission has been achieved and usually includes ATRA. This strategy is based on decreased relapse rates at 3 years seen with the addition of ATRA in the PETHEMA LPA99 study (8.7% vs 20.1% without ATRA, p=0.004).43, 44 For patients who received anthracycline-based induction therapy, at least two cycles of ATRA-anthracycline combination therapy should be administered. Either idarubicin or daunorubicin may be used, and ATRA is given for 1–2 weeks of each cycle. For patients who received induction with arsenic and ATRA, the same agents may be used for consolidation up to six cycles.44

Maintenance

Maintenance consists of 6-mercaptopurine and methotrexate, given in combination with ATRA. A reduction in relapse rates at 2 years was seen when all three agents were used together: ATRA plus 6-mercaptopurine and methotrexate (8%), 6-mercaptopurine and methotrexate (13%), ATRA alone (21%), and no maintenance (35%). Maintenance therapy is usually continued for 2 years.44, 47

Relapse

Arsenic, either alone or in combination with ATRA, may be used for hematologic or molecular relapse.44 Complete remission rates up to 92% and a molecular remission rate of 73% have been reported with arsenic alone.48–49 Combination ATRA and arsenic may be used in patients who did not receive an arsenic-containing induction regimen.44 Gemtuzumab ozogamicin is another option for patients who have relapsed. Molecular remission rates of 91% and 100% were achieved after patients received two and three doses of gemtuzumab, respectively.44, 45 Gemtuzumab is the recommended therapy for patients who have a molecular relapse within 6 months of arsenic-based induction therapy or who fail ATRA-arsenic salvage therapy.44

Differentiating Agents

All-trans-Retinoic Acid

This agent is a retinoid that induces differentiation of abnormal promyelocytes. It has a distinct adverse-effect profile that includes retinoic acid syndrome (RAS; discussed in a later section). Other adverse effects of ATRA include arrhythmias, headache, dizziness, visual disturbances, and rash.50 Also worth noting is that the mucosal membrane dryness associated with ATRA may predispose the pregnant patient to vaginal rupture and hemorrhage during labor.17

Although experience with ATRA in pregnant patients is limited, the retinoids are known to be potent teratogens. Increased rates of spontaneous abortion and major fetal abnormalities have been reported. These abnormalities involve the musculoskeletal, cardiovascular, and central nervous systems, as well as the ears, eyes, and thymus. In addition, facial dysmorphia, cleft palate, parathyroid hormone deficiency, and low
Table 1. Case Reports of Treatment of Acute Promyelocytic Leukemia During Pregnancy

<table>
<thead>
<tr>
<th>Mother’s Age at Diagnosis (yrs)</th>
<th>Gestational Age (wks)</th>
<th>At Diagnosis</th>
<th>At Delivery</th>
<th>Chemotherapy Regimen</th>
<th>Delivery Method</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>First trimester</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>18</td>
<td>18</td>
<td>8</td>
<td>39</td>
<td>Daunorubicin 96 mg/day; prednisone 90 mg/day; then maintenance with cytarabine 120 mg once every 10 days</td>
<td>Vaginal</td>
</tr>
<tr>
<td>22</td>
<td>22</td>
<td>Conception</td>
<td>34</td>
<td>Daunorubicin 30 mg/m²/day on days 1–2; methylglyoxalbisguanyl-hydrazone 250 mg/m³/day on days 3, 5, and 8</td>
<td>Vaginal</td>
</tr>
<tr>
<td>26</td>
<td>26</td>
<td>Conception</td>
<td>34</td>
<td>Doxorubicin, cytarabine, vincristine</td>
<td>Therapeutic abortion</td>
</tr>
<tr>
<td>36</td>
<td>36</td>
<td>Conception</td>
<td>34</td>
<td>Cytarabine 80 mg x 11 doses, daunorubicin 40 mg x 1 dose, 6-thioguanine 80 mg x 5 doses (maintenance therapy)</td>
<td>Cesarean</td>
</tr>
<tr>
<td>18 (relapsed APL)</td>
<td>NR</td>
<td>NR</td>
<td>32</td>
<td>ATRA 45 mg/m³/day, prednisone 1 mg/kg/day</td>
<td>Cesarean</td>
</tr>
<tr>
<td>28</td>
<td>28</td>
<td>14</td>
<td>40</td>
<td>ATRA 45 mg/m³/day x 60 days; filgrastim 75 µg/day s.c. on days 4–10; epoetin alfa 2000 units 3 times/wk on days 10–37</td>
<td>Cesarean</td>
</tr>
<tr>
<td>NR</td>
<td>NR</td>
<td>Diagnosis</td>
<td>NR</td>
<td>Doxorubicin, cytarabine, vincristine, prednisone (maintenance), discontinued at 8 wks’ gestation</td>
<td>NR</td>
</tr>
<tr>
<td>31</td>
<td>31</td>
<td>9</td>
<td>NA</td>
<td>Daunorubicin, cytarabine, 6-thioguanine</td>
<td>Therapeutic abortion</td>
</tr>
<tr>
<td>28</td>
<td>28</td>
<td>13</td>
<td>36</td>
<td>Idarubicin 12 mg/m³/day x 3 days, ATRA 45 mg/m³/day x 2 cycles, then consolidation with idarubicin 12 mg/m³/day x 2 days and ATRA daily x 2 cycles</td>
<td>Cesarean</td>
</tr>
<tr>
<td>28</td>
<td>28</td>
<td>7</td>
<td>NA</td>
<td>ATRA, daunorubicin, cytarabine</td>
<td>Spontaneous abortion</td>
</tr>
<tr>
<td>33</td>
<td>33</td>
<td>9</td>
<td>NA</td>
<td>ATRA, daunorubicin, cytarabine</td>
<td>Therapeutic abortion</td>
</tr>
<tr>
<td>38</td>
<td>38</td>
<td>5</td>
<td>NA</td>
<td>ATRA, daunorubicin, cytarabine</td>
<td>Therapeutic abortion</td>
</tr>
<tr>
<td><strong>Second trimester</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>33</td>
<td>33</td>
<td>26</td>
<td>34</td>
<td>Daunorubicin, cytarabine, 6-thioguanine</td>
<td>Vaginal</td>
</tr>
<tr>
<td>18</td>
<td>18</td>
<td>21</td>
<td>30</td>
<td>Cytarabine 100 mg/m³/day on days 1–9, doxorubicin 70 mg/m³/day on days 1–3, 6-thioguanine 100 mg/m³/day on days 1–9, prednisone 40 mg/m³/day on days 1–9, vincristine 1 mg/m³/day on days 1 and 9</td>
<td>Cesarean</td>
</tr>
<tr>
<td>30</td>
<td>30</td>
<td>22</td>
<td>28</td>
<td>Doxorubicin 25 mg/m³/day on days 1–3, cytarabine 100 mg/m³ x 12h on days 1–7, 6-thioguanine 100 mg/m³ x 12h on days 1–7</td>
<td>Cesarean</td>
</tr>
<tr>
<td>22</td>
<td>22</td>
<td>26</td>
<td>30</td>
<td>ATRA 45 mg/m³/day x 30 days (during pregnancy)</td>
<td>Cesarean</td>
</tr>
<tr>
<td>34</td>
<td>34</td>
<td>23</td>
<td>32</td>
<td>ATRA 45 mg/m³/day x ~28 days, followed by 50% dose reduction secondary to elevated hepatic enzyme levels</td>
<td>Vaginal</td>
</tr>
<tr>
<td>30</td>
<td>30</td>
<td>28</td>
<td>32</td>
<td>ATRA 45 mg/m³/day x ~23 days (during pregnancy)</td>
<td>Cesarean</td>
</tr>
<tr>
<td>29</td>
<td>29</td>
<td>25</td>
<td>34</td>
<td>Cytarabine 10 mg/kg/day on days 1 and 10, daunorubicin 1.5 mg/kg/day on days 2 and 11, mitoxantrone 12 mg/m³/day on days 3 and 12, 6-thioguanine 100 mg/m³ x 12h on days 1, 2, 10, and 11</td>
<td>Cesarean</td>
</tr>
<tr>
<td>28</td>
<td>28</td>
<td>20</td>
<td>34</td>
<td>Cytarabine 10 mg/kg/day on days 1 and 10, daunorubicin 1.5 mg/kg/day on days 2 and 11, mitoxantrone 12 mg/m³/day on days 3 and 12, 6-thioguanine 100 mg/m³ x 12h on days 1, 2, 10, and 11</td>
<td>Cesarean</td>
</tr>
</tbody>
</table>
Table 1. (continued)

<table>
<thead>
<tr>
<th>Fetal Outcome</th>
<th>Maternal Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>3050-g healthy infant</td>
<td>Complete remission after chemotherapy; died 33 days postpartum</td>
</tr>
<tr>
<td>2200-g healthy infant</td>
<td>Complete remission for at least 7 mo</td>
</tr>
<tr>
<td>Aborted fetus</td>
<td>Complete remission for at least 3.5 yrs</td>
</tr>
<tr>
<td>2800-g infant intubated for severe respiratory distress; bilateral pneumothorax; craniofacial anomalies; bilateral four-finger hands with hypoplastic thumbs; retarded motor milestones noted at 13 mo 1820-g infant with jaundice and respiratory distress syndrome at birth; normal growth and development reported at 15 mo</td>
<td>Complete remission after induction chemotherapy</td>
</tr>
<tr>
<td>Healthy infant</td>
<td></td>
</tr>
<tr>
<td>Aborted fetus</td>
<td>DIC on diagnosis of APL; subsequent second complete remission noted; second relapse at 30 wks' gestation; died of infectious complications</td>
</tr>
<tr>
<td>3050-g healthy infant</td>
<td>Complete remission for at least 12 mo</td>
</tr>
<tr>
<td>2200-g healthy infant</td>
<td></td>
</tr>
<tr>
<td>1820-g infant with jaundice and respiratory distress syndrome at birth; normal growth and development reported at 15 mo</td>
<td>DIC on diagnosis of APL; subsequent second complete remission noted; second relapse at 30 wks' gestation; died of infectious complications</td>
</tr>
<tr>
<td>2200-g healthy infant</td>
<td>Complete remission for at least 7 mo</td>
</tr>
<tr>
<td>Aborted fetus</td>
<td>Complete remission for at least 27 mo</td>
</tr>
<tr>
<td>2720-g infant required bag-mask ventilation for 15 sec after delivery; asymptomatic right-sided dilated cardiomyopathy with preserved left ventricular function; normal 6-wk follow-up with resolution of cardiomyopathy</td>
<td>Preeclampsia during pregnancy; complete remission after 2 cycles of treatment</td>
</tr>
<tr>
<td>Aborted fetus</td>
<td>Complete remission</td>
</tr>
<tr>
<td>Aborted fetus</td>
<td>Complete remission</td>
</tr>
<tr>
<td>2470-g healthy infant</td>
<td>Complete remission; BMT 3 mo postpartum; died 16 mo postpartum of pneumonia while in complete remission</td>
</tr>
<tr>
<td>1320-g infant with respiratory distress; no complications reported 70 days after delivery</td>
<td>Complete remission for at least 4 mo</td>
</tr>
<tr>
<td>1140-g healthy infant</td>
<td>Complete remission for at least 20 mo</td>
</tr>
<tr>
<td>Cardiac arrhythmia and cardiac arrest immediately after delivery followed by successful resuscitation</td>
<td>Morphologic complete remission</td>
</tr>
<tr>
<td>Premature delivery of healthy twins with normal weight for gestational age (1975 g, 1850 g) and normal development; one infant required continuous positive airway pressure for a few days; no signs of impairment at 8 mo 2380-g infant with respiratory distress; normal growth and development at 5 mo 2220-g healthy infant</td>
<td>Excessive peri- and postnatal bleeding noted; complete remission for at least 7 mo</td>
</tr>
<tr>
<td>2100-g healthy infant</td>
<td>DIC on diagnosis of APL; complete remission obtained</td>
</tr>
<tr>
<td></td>
<td>DIC on diagnosis of APL; complete remission obtained; underwent allogeneic BMT; died 8 mo later in relapse</td>
</tr>
</tbody>
</table>

DIC = disseminated intravascular coagulation; APL = acute promyelocytic leukemia; BMT = bone marrow transplantation; NR = not recorded; mo = month; wks = weeks; yrs = years; yrs. = year(s); completes = completed; symptom(s) = symptom(s) present; NR = not recorded; mo = month; wks = weeks; yrs = years; yrs. = year(s); completes = completed; symptom(s) = symptom(s) present;
Table 1. Case Reports of Treatment of Acute Promyelocytic Leukemia During Pregnancy (continued)

<table>
<thead>
<tr>
<th>Mother’s Age at Diagnosis (yrs)</th>
<th>Gestational Age (wks)</th>
<th>Chemotherapy Regimen</th>
<th>Delivery Method</th>
</tr>
</thead>
<tbody>
<tr>
<td>Second trimester</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>29[30]</td>
<td>23</td>
<td>Daunorubicin on days 9-11, ATRA 45 mg/m²/day continuous</td>
<td>Vaginal</td>
</tr>
<tr>
<td>21[31]</td>
<td>21</td>
<td>Cytarabine and daunorubicin at 21 and 25 wks’ gestation;</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>cytarabine and mitoxantrone at 28 wks’ gestation</td>
<td>Cesarean</td>
</tr>
<tr>
<td>36[22]</td>
<td>24</td>
<td>ATRA 45 mg/m²/day, then 2 cycles of cytarabine 100 mg/m² b.i.d. x 7 days and daunorubicin 45 mg/m²/day x 3 days</td>
<td>NR</td>
</tr>
<tr>
<td>29[22]</td>
<td>20</td>
<td>Cytarabine 160 mg b.i.d. x 7 days, daunorubicin 60 mg/day x 3 days, ATRA 45 mg/m² t.i.d. x 30 days</td>
<td>NR</td>
</tr>
<tr>
<td>23[23]</td>
<td>21</td>
<td>ATRA 45 mg/m²/day x 40 days; 6-thioguanine, cytarabine,</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>and daunorubicin started on day 10; cytarabine 1000 mg/m²/day and mitoxantrone started on day 40</td>
<td>Vaginal</td>
</tr>
<tr>
<td>41[24]</td>
<td>25</td>
<td>ATRA 45 mg/m²/day x 56 days (during pregnancy)</td>
<td>Cesarean</td>
</tr>
<tr>
<td>16[25]</td>
<td>19</td>
<td>Daunorubicin, cytarabine, 6-thioguanine</td>
<td>NR</td>
</tr>
<tr>
<td>35[26]</td>
<td>21</td>
<td>Idarubicin 12 mg/m²/day on days 2, 4, 6, and 8, and</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>ATRA 45 mg/m²/day; consolidation with idarubicin 5 mg/m²/day and cytarabine 1000 mg/m²/day on days 1, 2, 3, and 4 and ATRA 45 mg/m²/day x 15 days</td>
<td>Cesarean</td>
</tr>
<tr>
<td>16[27]</td>
<td>25</td>
<td>Idarubicin, ATRA</td>
<td></td>
</tr>
<tr>
<td>37[28]</td>
<td>26</td>
<td>Daunorubicin 45 mg/m²/day, cytarabine 100 mg/m²/day</td>
<td>Spontaneous abortion</td>
</tr>
<tr>
<td>27[29]</td>
<td>28</td>
<td>ATRA</td>
<td>Vaginal</td>
</tr>
<tr>
<td>35[30]</td>
<td>25</td>
<td>Cytarabine, daunorubicin, and ATRA</td>
<td>NR</td>
</tr>
<tr>
<td>23[31]</td>
<td>21</td>
<td>ATRA, 6-mercaptopurine (maintenance therapy)</td>
<td>Vaginal</td>
</tr>
<tr>
<td>Third trimester</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>30[32]</td>
<td>30</td>
<td>Cytarabine and daunorubicin</td>
<td>Cesarean</td>
</tr>
<tr>
<td>36[33]</td>
<td>29</td>
<td>Daunorubicin 45 mg/m²/day x 3 days, cytarabine 100 mg/m²/day CIVI x 7 days</td>
<td>Vaginal</td>
</tr>
<tr>
<td>30[32]</td>
<td>30</td>
<td>ATRA 70 mg/day x 12 days (during pregnancy)</td>
<td>Cesarean</td>
</tr>
<tr>
<td>34[33]</td>
<td>34</td>
<td>ATRA 45 mg/m²/day x ~4 wks (during pregnancy)</td>
<td>Vaginal</td>
</tr>
<tr>
<td>29[34]</td>
<td>29</td>
<td>ATRA 45 mg/m²/day</td>
<td>Vaginal</td>
</tr>
<tr>
<td></td>
<td>29 (delivery ~42 hrs after ATRA started)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>37[35]</td>
<td>29</td>
<td>ATRA 45 mg/m²/day x ~26 days (during pregnancy)</td>
<td>Cesarean</td>
</tr>
<tr>
<td>19[36]</td>
<td>32</td>
<td>ATRA 45 mg/m²/day x ~14 days (during pregnancy)</td>
<td>Vaginal</td>
</tr>
<tr>
<td>30[37]</td>
<td>29</td>
<td>ATRA 45 mg/m²/day</td>
<td>Cesarean</td>
</tr>
<tr>
<td>29[37]</td>
<td>31</td>
<td>ATRA 45 mg/m²/day</td>
<td>Cesarean</td>
</tr>
</tbody>
</table>

NA = not applicable; NR = not reported; APL = acute promyelocytic leukemia; ATRA = all-trans-retinoic acid; DIC = disseminated intravascular coagulation; RAS = retinoic acid syndrome; BMT = bone marrow transplantation; CIVI = continuous intravenous infusion; ARDS = acute respiratory distress syndrome.
IQ scores (with and without obvious central nervous system abnormalities) have been reported. A 25-fold relative risk of major craniofacial, otologic, cerebral, and

<table>
<thead>
<tr>
<th>Fetal Outcome</th>
<th>Maternal Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>2765-g infant with moderate hyperbilirubinemia and subependymal hemorrhages; discharged in good condition 10 days after birth</td>
<td>DIC on diagnosis of APL; RAS during APL treatment; complete remission for at least 2 mo NR</td>
</tr>
<tr>
<td>857-g (low-birth-weight) preterm infant intubated for respiratory distress; bone marrow aplasia, bilateral hydronephrosis, intracranial hemorrhage, hyponatremia, hypoglycemia, seizures, failure to thrive noted; discharged at 4.5 mo after progressive weight gain</td>
<td>Partial remission; relapse 6 mo postpartum; extensive retinal hemorrhage and coma; died</td>
</tr>
<tr>
<td>2300-g healthy infant; normal development at 10 mo</td>
<td>Complete remission</td>
</tr>
<tr>
<td>2200-g (low-birth-weight) premature infant intubated for respiratory distress; normal development at 5 mo</td>
<td>Septicemia during pregnancy; complete remission obtained</td>
</tr>
<tr>
<td>2490-g healthy infant; normal development reported at 4 mo</td>
<td>Complete remission for at least 9 mo</td>
</tr>
<tr>
<td>2610-g healthy infant</td>
<td>Complete remission for at least 25 yrs</td>
</tr>
<tr>
<td>Healthy infant</td>
<td>DIC and hyperleukocytosis during APL therapy; morphologic complete remission after induction; molecular remission after first consolidation</td>
</tr>
<tr>
<td>1950-g (low-birth-weight) premature infant; noted abnormalities</td>
<td>Febrile neutropenia, hemorrhagic complications including right frontal lobe hemorrhage, cranial nerve palsy, seizures, severe mucositis, respiratory distress requiring ventilation noted during pregnancy; complete remission obtained</td>
</tr>
<tr>
<td>Healthy infant</td>
<td>Died while pancytopenic</td>
</tr>
<tr>
<td>1050-g premature infant; died of intracranial bleeding on day 22 of APL therapy</td>
<td>Complete remission</td>
</tr>
<tr>
<td>2490-g premature infant; fetal distress; normal growth and development at 9 mo</td>
<td>Complete remission for at least 20 mo</td>
</tr>
<tr>
<td>2100-g healthy infant</td>
<td>DIC on diagnosis of APL; ARDS postpartum; complete remission, relapsed 7 mo later; second complete remission after reinduction; underwent allogeneic BMT; died of varicella infection</td>
</tr>
<tr>
<td>Intrauterine fetal death on day 4 of chemotherapy</td>
<td>DIC on diagnosis of APL; RAS during APL therapy; complete remission obtained</td>
</tr>
<tr>
<td>Fetal distress syndrome noted on day 9 of ATRA therapy; 2080-g healthy infant born</td>
<td>DIC on diagnosis of APL; complete remission for at least 9 mo</td>
</tr>
<tr>
<td>4000-g healthy infant; low levels of isotretinoin and 4-oxo-isotretinoin detected in umbilical cord blood, but no levels of tretinoin (ATRA) or 4-oxo-tretinoin detected</td>
<td>Vaginal bleeding on diagnosis of APL; complete remission for at least 20 mo</td>
</tr>
<tr>
<td>Death (fetus diagnosed with Potter's syndrome during first trimester)</td>
<td>Complete remission</td>
</tr>
<tr>
<td>1904-g (low-birth-weight) infant with arrhythmia; normal development with discharge 34 days after birth</td>
<td>Died</td>
</tr>
<tr>
<td>1980-g (low-birth-weight) infant; normal development at 4 yrs</td>
<td>Complete remission</td>
</tr>
<tr>
<td>2318-g infant required intubation for respiratory distress syndrome; normal growth and development at 12 mo of follow-up</td>
<td>Complete remission</td>
</tr>
<tr>
<td>1634-g (low-birth-weight) infant required intubation for respiratory distress syndrome; patent ductus arteriosus; ATRA detected in plasma; normal growth and development at 36 mo of follow-up</td>
<td>Complete remission</td>
</tr>
</tbody>
</table>
cardiovascular abnormalities has been described with the administration of 13-cis-retinoic acid in the first trimester of pregnancy.\textsuperscript{17} It was not until 1994 that the use of ATRA for the treatment of APL in the second and third trimesters was first described in the literature.\textsuperscript{16,17} In a case report of a 22-year-old woman with a diagnosis of APL during the 26th week of pregnancy, therapy with ATRA 45 mg/m\textsuperscript{2}/day was prescribed for approximately 30 days, and a cesarean delivery was performed at 30 weeks’ gestation.\textsuperscript{16} The infant sustained cardiac arrest immediately after delivery but was successfully resuscitated. The patient continued to make satisfactory progress before being discharged from the hospital. The patient’s bone marrow aspirate, which was obtained after delivery, revealed a morphologic complete remission.

Another case report described a 34-year-old woman with a diagnosis of APL in her 23rd week of pregnancy.\textsuperscript{17} Induction therapy with ATRA 45 mg/m\textsuperscript{2}/day was started. Morphologic complete remission was noted on day 28 of therapy. The patient’s course was relatively uncomplicated with the exception of gingival hypertrophy and mild elevation of hepatic enzyme levels. The patient underwent spontaneous vaginal delivery at 32 weeks’ gestation. She delivered premature twins with no noted abnormalities. Daunorubicin and cytarabine were administered approximately 2 months after a complete remission was obtained (4 wks after delivery). The patient continued to receive three additional consolidation courses of chemotherapy and remained in complete remission.

A retrospective series reviewed both the use of single-agent ATRA and combination ATRA-chemotherapy for the treatment of APL during pregnancy.\textsuperscript{3} Three patients received ATRA in combination with daunorubicin and cytarabine, and one patient received single-agent ATRA. All three patients who received combination therapy were diagnosed and treated during the first trimester. Two of these patients elected to undergo therapeutic abortions, and the third patient had a miscarriage. The gestational weeks at which these events occurred were not noted in the article. The patient who received single-agent ATRA was diagnosed and treated at 28 weeks’ gestation. She had a full-term pregnancy with normal delivery. All four patients achieved complete remission after induction therapy.

A study was conducted to quantify plasma ATRA levels in neonates whose mothers received ATRA in the third trimester.\textsuperscript{35,37} Of the three cases included in this study, ATRA was detected in umbilical cord blood in only one case. All three neonates experienced respiratory distress at birth. One neonate had premature atrial contractions, whereas another had patent ductus arteriosus. However, all three neonates had normal development and growth in their respective follow-up periods (3, 12, and 36 mo).

Most of the case reports, including the aforementioned cases, suggest that ATRA is relatively safe for both mother and fetus when
used in the second and third trimesters (Table 1). Relatively favorable fetal outcomes were reported in 17 of 20 cases of ATRA given in the second and third trimesters, including the births of five healthy infants and one set of healthy premature twins. Transient complications at birth, such as respiratory distress and cardiac arrhythmia, were seen in 10 of these cases but resolved on discharge. In contrast, three of the six cases in the first trimester reported negative fetal outcomes. One patient had a miscarriage, and two patients elected to undergo therapeutic abortion.

Complete remission was noted for all but three patients who received ATRA (one partial remission, two deaths before achieving a response). The most common adverse effects reported included RAS, hyperleukocytosis, transient transaminitis, and headache. There was one report of septicemia during chemotherapy administration.

Arsenic Trioxide

The proposed mechanisms of action of arsenic trioxide include induction of partial cell differentiation through PML-RARα degradation and apoptosis. Adverse effects include nausea, vomiting, headache, fatigue, neuropathy, myelosuppression, fluid retention, and hypokalemia. More severe adverse effects associated with arsenic include QT-interval prolongation and RAS.

We found no published cases that reviewed the use of arsenic trioxide for the treatment of APL in pregnancy. However, it is known that arsenic passes through the human placenta, and in various animal species, high doses of arsenic may adversely affect the developing fetus. A recent study evaluated the effect of arsenic in drinking water on fetal and infant survival. The authors prospectively evaluated 29,134 pregnancies during 1991–2000 in Bangladesh. Consumption of drinking water containing arsenic levels above the Bangladesh standard (> 50 µg/L) during pregnancy was associated with a 17% increased risk of infant death and a 14% increased risk of fetal loss. In another prospective study on the effects of arsenic-contaminated drinking water on pregnancy in Bangladesh, arsenic levels in keratin-rich tissues, such as hair and toenails, of the mother and newborn were evaluated. An inverse correlation between maternal arsenic exposure (as measured in maternal hair) and infant birth weight was found in this study. Infant birth weight decreased by 194 g for every 1-µg/g increase in arsenic exposure. Both of these studies suggest that arsenic is associated with adverse fetal outcomes.

**Antitumor Antibiotics**

**Antituberculosis**

Doxorubicin has been used in APL regimens, but to a lesser extent than idarubicin and daunorubicin. The primary antitumor activity of anthracyclines involves DNA intercalation. These drugs interfere with topoisomerase II.
activity by stabilizing the cleavable complexes that form between DNA and topoisomerase II, which inhibits the religation of cleaved DNA. Anthracyclines also generate free radicals, resulting in single- and double-stranded DNA breaks. Common adverse effects of anthracyclines include nausea, vomiting, alopecia, myelosuppression, and cardiotoxicity.

Although the anthracyclines are known to have mutagenic and carcinogenic effects in vitro and in animals, their potential toxicity in the human fetus is unclear. Cardiotoxicity is a well-known major adverse effect, and it can manifest as arrhythmia, cardiomyopathy, or heart failure. As idarubicin is more lipophilic than the other anthracyclines, there is a theoretic concern that increased placental transfer of idarubicin may result in increased fetal and infant cardiotoxicity. In one case of idarubicin administration in the first trimester, APL was diagnosed at 13 weeks' gestation. Idarubicin-ATRA combination therapy (four cycles of idarubicin and continuous ATRA) was started at 14 weeks' gestation and continued until 32 weeks' gestation. At birth, transient asymptomatic right-sided dilated cardiomyopathy was diagnosed in the infant. At the infant's 6-week follow-up examination, no clinical signs of heart failure were detected, and the echocardiogram revealed complete resolution of the cardiomyopathy with normal cardiac function.

A retrospective review of 160 patients with hematologic and nonhematologic malignancies who received anthracyclines during pregnancy was conducted. Three cases of fetal cardiotoxicity were observed in the second and third trimesters, which included one case of reversible intermittent sinusoidal fetal heart and two cases of myocardial distress. The authors also reported a higher frequency of fetal malformations in the first trimester. Fetal death more commonly occurred in patients with leukemia (87%) and in those who received daunorubicin (73%). Six (40%) of the 15 fetal deaths were associated with maternal death. The authors concluded that progressive maternal disease had a strong association with fetal death and may account for an increased occurrence of this outcome in patients with acute leukemia. The authors further noted that maternal disease progression is a major risk for the fetus in a patient with leukemia; therefore, chemotherapy should not be delayed.

Additional reports of anthracycline exposure in combination with other chemotherapy agents during the first, second, and third trimesters of pregnancy for the treatment of APL have been described in the literature (Table 1). Although most of these cases reported delivery of healthy infants, adverse events were also reported and included spontaneous abortion, intrauterine fetal death, prematurity, atrial septum defect and other congenital anomalies, cardiomyopathy, pulmonary hypoplasia, fetal malformations, and poor overall growth. However, an increased frequency of adverse fetal outcomes was seen in the first trimester. Seven of the 10 cases in which patients received an anthracycline in the first trimester reported fetal malformations (two cases) or fetal demise (five cases). The patient underwent a therapeutic abortion in four of the five cases in which fetal demise occurred. The previously mentioned case of first-trimester idarubicin administration was the only case report of infant cardiotoxicity associated with exposure to an anthracycline-containing APL regimen in utero.

In contrast, relatively favorable outcomes were reported in most cases (12 of 17 cases) in which patients were exposed to an anthracycline in the second or third trimester, including eight healthy infants at birth. Complete remission was reported for all but five patients who received an anthracycline (one partial remission, two not reported, two deaths before achieving a response). Infection and mucositis were among the reported patient complications.

**Anthracyclines**

Mitoxantrone is a topoisomerase II inhibitor that has been incorporated into the consolidation phase for certain APL regimens (PETHEMA LPA94 and LPA99 regimens) and infrequently as part of induction. It is an anthracyclene, an anthracycline-like derivative, which is reported to have less cardiotoxic effects than the anthracyclines (mitoxantrone 2.2–3.5% vs anthracyclines 5–65%). Decreased free radical formation and increased calcium release from myocardial cells are the suggested mechanisms for the reduced cardiotoxicity seen with mitoxantrone.

Four cases of mitoxantrone exposure during the treatment of APL during pregnancy have been reported in the literature. One case involved the administration of mitoxantrone for consolidation. The patient received induction with daunorubicin, ATRA, 6-thioguanine, and...
cytarabine at 21 weeks' gestation. Consolidation therapy with mitoxantrone and cytarabine was started once complete remission was obtained (26 wks' gestation). A healthy infant was born at 35 weeks' gestation. Another group reported normal fetal outcomes for two patients who received mitoxantrone in the second trimester, as part of their induction therapy. Both of these patients also achieved complete remission. The fourth case was a patient with APL who received daunorubicin and cytarabine at 21 and 25 weeks' gestation. Because of an inadequate response, treatment was changed to mitoxantrone and cytarabine at 28 weeks' gestation. An 857-g infant was born prematurely by cesarean delivery at 29 weeks' gestation. Fetal complications included respiratory distress requiring mechanical ventilation at delivery, bone marrow aplasia, bilateral hydronephrosis, intracranial hemorrhage, hyponatremia, hypoglycemia, and seizures. The infant had a prolonged hospital course and was not discharged until 4.5 months later. Response to chemotherapy was not reported for this patient.

Antimetabolites

Folic Acid Antagonists

Methotrexate inhibits dihydrofolate reductase, the enzyme that converts folic acid to the active tetrahydrofolate form. This results in inhibition of both thymidylate synthetase and purine nucleotide synthesis, with subsequent inhibition of DNA replication. Common adverse effects of methotrexate include mucositis, myelosuppression, nausea, and hepatotoxicity. Unlike other chemotherapy agents in this review, methotrexate displays unusual distribution pharmacokinetics that may increase fetal exposure to this agent. The drug distributes into third-space compartments, such as pleural and ascitic fluid, potentially resulting in delayed elimination. Since amniotic fluid is a third-space compartment, the duration of fetal exposure and risk of teratogenic effects from methotrexate may be increased.

Case reports of methotrexate in pregnant patients with leukemia have been primarily with the treatment of acute leukemia subtypes other than APL. A normal fetal outcome was observed in most of the cases. The timing of methotrexate administration varied in each case. One case reported fetal pancytopenia resulting from chemotherapy administration to a patient with acute lymphocytic leukemia. Treatment was administered in all three trimesters and included methotrexate, cytarabine, and 6-mercaptopurine. The infant died secondary to septicemia at age 21 days.

As compared with other chemotherapy agents, methotrexate administration in the first trimester has been more frequently associated with congenital abnormalities, fetal loss, and malformations. Many of these reports describe the use of methotrexate for nononcologic indications, such as rheumatoid arthritis and psoriasis. Based on these observations, it has been recommended that methotrexate be avoided during the first trimester.

Pyrimidine Analogs

Cytarabine incorporates into DNA and inhibits DNA polymerase, resulting in inhibition of DNA repair. Nausea, diarrhea, rash, fever, myelosuppression, conjunctivitis, and hepatotoxicity are among its more common adverse effects. Cerebellar toxicity may also be seen with high doses of cytarabine. One patient with APL was receiving maintenance therapy with cytarabine when the pregnancy was discovered. The first cycle, a combination of cytarabine and daunorubicin, was calculated to have been administered approximately on the date of conception. The second cycle, a combination of cytarabine and 6-thioguanine, was administered approximately 35–37 days after conception. After the pregnancy was known, maintenance chemotherapy was discontinued. The infant was delivered by cesarean birth on the expected date and was noted to have several craniofacial and limb anomalies. The craniofacial anomalies required surgical intervention at 10 and 46 weeks of age. At 13 months of age, the child was noted to be underweight, with mild generalized hypotonia and slightly retarded motor milestones.

Reports of cytarabine monotherapy are scarce. In one case report, a patient with acute lymphocytic leukemia was treated with cytarabine monotherapy during pregnancy. The patient received monthly cytarabine maintenance at approximately 4 and 8 weeks' gestation, and she delivered an infant with extremity and ear deformities. The authors mentioned that limb bud development usually occurs by the fourth week of gestation, and that by the sixth week, the buds become differentiated and are able to be recognized as individual appendages. The external ears are formed by the sixth week of gestation. The authors concluded
that the administration of cytarabine correlated well with the noted congenital abnormalities.

Several cases of cytarabine exposure during the first, second, and third trimesters of pregnancy for the treatment of APL have been reported (Table 1). For all of these cases, cytarabine was given in combination with other chemotherapy agents, including an anthracycline.3, 4, 6, 7, 10, 11, 13-15, 19, 21-23, 25, 27, 28, 30, 31 Adverse fetal events occurred in seven of eight cases with first-trimester cytarabine exposure; these included fetal malformations and spontaneous abortion. In addition, four patients elected to undergo therapeutic abortion.3, 4, 6, 7, 10, 11 A normal fetal outcome was seen in most of the second and third trimester cytarabine exposures (11 of 15 cases), which included eight healthy infants at birth.11, 13-15, 19, 21-23, 25, 27, 28, 30, 31 Complete remission was noted for most patients who received cytarabine (18 of 23 patients). Complications during pregnancy, including septicemia and varicella infection, were reported.3, 4, 6, 7, 10, 11, 13-15, 19, 21-23, 25, 27, 28, 30, 31

Purine Analogs

In addition to 6-mercaptopurine, 6-thioguanine has been used for maintenance therapy of APL. Both agents inhibit purine synthesis, which ultimately leads to inhibition of DNA and RNA synthesis. Adverse effects of the purine analogs include nausea, myelosuppression, and hepatotoxicity.34

Case reports involving the use of 6-mercaptopurine or 6-thioguanine for the treatment of APL during pregnancy are limited. Some of these reports included cases in which the diagnosis was made in the first trimester of pregnancy.7, 11 In a case previously described in this review, the patient received 6-thioguanine, cytarabine, and daunorubicin.7 The infant experienced severe respiratory distress, bilateral pneumothoraces, craniofacial and limb anomalies, and retarded motor milestones.

Other case reports of purine analogs for APL treatment during the second trimester of pregnancy have been described. Seven patients received 6-thioguanine in combination with other chemotherapy agents.11, 12-15, 19, 23 Normal infant growth and development were reported in all seven cases. A normal outcome was also reported for 6-mercaptopurine administration in the second trimester.29 All of the patients who received purine analogs in these cases achieved complete remission.7, 11, 13-15, 19-23, 29

Gemtuzumab Ozogamicin

Gemtuzumab ozogamicin is an anti-CD33 monoclonal antibody linked to the cytotoxic antibiotic calicheamicin. The CD33 is detected in essentially all APL cases.45 The overall cytotoxic effect of gemtuzumab is from the binding of calicheamicin to DNA, resulting in double-stranded DNA breaks. Common adverse effects include hepatotoxicity, infusion-related reactions, myelosuppression, nausea, and low-grade fever.45, 54 Venocclusive disease, which can be fatal, has also been reported at a frequency of 3–15%.54 To our knowledge, there are no published case reports of gemtuzumab exposure in pregnant women.

Complications of Acute Promyelocytic Leukemia

Disseminated Intravascular Coagulation

Disseminated intravascular coagulation is a common sequela of APL. It can cause life-threatening hemorrhage, especially after initiation of cytotoxic therapy. Approximately 3% of newly diagnosed patients will die of hemorrhage before treatment is started. Five percent of patients will die of hemorrhage during the first 3 weeks of induction therapy, with half of these patients dying in the first week of treatment.39

Four cases of DIC associated with APL and pregnancy have been described in detail.53-66 In these cases, DIC occurred after delivery, placental abruption, or spontaneous abortion. The diagnosis of DIC also led to the diagnosis of APL in these patients. Two cases of postpartum APL-related DIC have been reported.63, 64 In both cases, DIC was managed with blood and platelet transfusions, and fresh frozen plasma. One patient later received ATRA and chemotherapy for APL.65 However, the condition of the other patient rapidly deteriorated, and she died 48 hours after presentation.64 Another report was that of a woman with placental abruption in the 25th week of gestation.65 The infant was stillborn, and the patient developed DIC shortly thereafter. Supportive care was given for DIC, and an abnormal blood smear subsequently led to a diagnosis of APL. The patient later received induction chemotherapy with ATRA, cytarabine, and daunorubicin. Another patient was admitted for genital bleeding during the sixth week of gestation.66 The patient subsequently had a spontaneous abortion. Peripheral blood smears
led to a concomitant diagnosis of DIC and APL. Later, DIC was managed with uterine embolization, and APL was treated with an anthracycline-based regimen.

General management of DIC in the setting of APL includes the administration of platelet transfusions to maintain a platelet count of 50 x 10^3/mm^3 or above, cryoprecipitate to replace fibrinogen, and fresh frozen plasma to replace clotting factors until the coagulopathy resolves. The clinical benefit of drugs such as heparin or tranexamic acid has not been determined.44 Although there are no specific guidelines on managing DIC in the pregnant patient, close monitoring of coagulation factors (prothrombin time, partial thromboplastin time, fibrinogen, D-dimer), especially in the first few weeks after the diagnosis of APL, is imperative.

Retinoic Acid Syndrome

Retinoic acid syndrome, otherwise known as APL differentiation syndrome, may occur with the administration of either ATRA or arsenic.50, 51 The frequency of RAS ranges from 2–27%. Typically, RAS occurs between the second day and third week of treatment, and it can be a life-threatening event, with a mortality rate of 2%. A defining characteristic of this syndrome is hyperleukocytosis. Patients with RAS may also have dyspnea, pericardial and pleural effusions, edema, weight gain, acute renal failure, and fever at presentation. Symptoms of capillary leak, manifesting as acute respiratory distress or an endotoxic shock–like picture, may also occur. It is thought that the cytokine release from differentiating promyelocytes leads to RAS.67

High doses of corticosteroids are imperative for the management of RAS. Dexamethasone 10 mg twice/day for 3–5 days, followed by a slow taper over 14 days, is recommended. If symptoms are mild, ATRA may be continued concomitantly with steroids, with close monitoring for progression of symptoms. If symptoms are severe or persistent, ATRA may be temporarily discontinued until symptoms resolve.44

Although some case reports have mentioned the occurrence of RAS in pregnant patients with APL, the management of RAS in this patient population has not been fully described. However, fetal exposure to steroids has been well documented in the literature, as antenatal steroid administration is the standard of care for women who are at risk for preterm delivery. Steroids have been shown to enhance fetal lung maturity, and reduce neonatal respiratory distress, intraventricular hemorrhage, and death.56–70

Treatment Strategies

Acute promyelocytic leukemia is highly curable, with reported complete remission rates up to 96%.41 Of note, complete remission was achieved by most patients in the case reports evaluated for this review. Although cure is the overall goal for a patient with APL, pregnancy forces the patient and clinician to make treatment decisions that incorporate fetal well-being.

Published case reports are the primary tools to assist the clinician in making an informed decision about the treatment of APL during pregnancy. When evaluating the literature, several limitations should be considered. First, case reports are not controlled for other factors that may have contributed to the reported adverse fetal outcomes, such as a predisposition toward miscarriage or certain congenital anomalies (e.g., cleft palate). Second, most patients received a combination of chemotherapy agents; therefore, distinguishing the teratogenic effects of one agent from another is difficult. Finally, there is limited literature on the long-term follow-up of children exposed in utero to chemotherapy. Although normal fetal outcomes have been reported, whether these children continued to be free of any adverse sequelae years after exposure to chemotherapy is not known.

Despite these limitations, some generalizations from the available literature may be extracted. Much of the data with ATRA suggest that it may yield relatively favorable fetal outcomes when administered in the second and third trimesters. Similar outcomes are also noted with the anthracyclines, mitoxantrone, cytarabine, and purine analogs. Aside from cardiac arrhythmia, intrauterine growth restriction, and prematurity, most infants were born without major defects. There were five reported cases of prematurity, six cases of low birth weight (adjusted for gestational age), and two cases of arrhythmia.16, 17, 21, 22, 25, 28, 29, 35–37, 71 Of note, both cases of cardiac arrhythmia occurred with single-agent ATRA.16, 35

In contrast, most pregnancies associated with ATRA and other chemotherapy agents in the first trimester ended in either spontaneous or elective abortion. Additional unfavorable outcomes, including craniofacial and limb abnormalities, were also noted. Since the critical period of organogenesis occurs during the first trimester,
spontaneous abortion and fetal malformations would be expected.

When treating a pregnant patient with APL, a number of issues need to be considered. Since APL is a medical emergency, treatment should not be delayed. Hemorrhage is a common cause of mortality in the first few weeks after the diagnosis of APL, and the early administration of ATRA has been associated with dramatic improvements in DIC-related coagulopathy. Furthermore, delays in treatment may result in leukemia progression, which may lead to maternal and subsequent fetal mortality.

As different outcomes have been reported in each trimester, APL treatment during pregnancy should be tailored to the gestational age of the fetus. In addition, the patient’s views on therapeutic abortion should be discussed, particularly if APL is diagnosed in the first trimester. If the patient decides to undergo therapeutic abortion, then extra precautions should be taken to minimize the risk of hemorrhage (i.e., maintaining platelet count above $50 \times 10^3/\text{mm}^3$, intensive monitoring of coagulation factors). After pregnancy termination, APL can be treated in the same way as for nonpregnant patients.

First Trimester

In the nonpregnant patient with APL, options for induction typically include ATRA in combination with either arsenic trioxide or an anthracycline (idarubicin or daunorubicin). However, treatment must be modified for the patient who chooses to continue her pregnancy. The agent ATRA should be avoided in the first trimester, as it is a known teratogen. Close monitoring and appropriate management of bleeding complications are especially important in this situation, since an increased DIC risk may result from the exclusion of ATRA. Arsenic trioxide should not be given at all during pregnancy. This is based on the lack of published reports of antenatal arsenic trioxide administration, as well as the unfavorable fetal outcomes associated with exposure to arsenic-contaminated water during pregnancy.

Single-agent anthracycline may be used as induction treatment in the first trimester. Although cardiotoxicity is a major complication of the anthracyclines, first-trimester exposure has not been associated with increased reports of fetal cardiomyopathy or arrhythmia. Nonetheless, fetal cardiac monitoring should be performed more frequently during pregnancy (i.e., every 1–2 wks). In addition, both the patient and clinician should be aware of the potential risks of fetal malformations and miscarriage with anthracycline administration in the first trimester. Daunorubicin is preferred over idarubicin as the anthracycline of choice. Because of its lipophilic nature, idarubicin is more likely to cross the placenta, which may theoretically increase the risk of cardiotoxicity.

Other chemotherapy agents should not be administered in the first trimester. Methotrexate, cytarabine, and purine analogs should be avoided, as fetal loss and teratogenic effects have been associated with exposure to these agents in the first trimester. In fact, methotrexate should not be given at all during pregnancy, since it distributes into third spaces, including amniotic fluid, potentially leading to decreased clearance and increased toxicity. Because of its adverse-effect profile and the lack of published reports of its use during pregnancy, gemtuzumab should also be avoided during pregnancy.

Second and Third Trimesters

Given the relatively favorable fetal outcomes that have been reported, combination ATRA-daunorubicin therapy may be given as induction in the second or third trimester. Since cardiac toxicity was noted for both ATRA and anthracyclines, fetal cardiac status should be frequently monitored throughout pregnancy. In addition, it is important to closely monitor for and rapidly treat RAS, where hyperleukocytosis is the usual presenting sign.

Delivery of the fetus is another issue to consider in the second and third trimesters. If the fetus is at least 24 weeks’ gestational age, then the patient may choose a cesarean delivery, before starting chemotherapy. Otherwise, vaginal delivery is preferred, due to increased bleeding risk from cesarean delivery. The nadir of most chemotherapy agents is 3 weeks. Therefore, to minimize bleeding and infectious complications, delivery should not occur until at least 3 weeks after chemotherapy administration. If necessary, antenatal steroids may be used to enhance fetal lung maturity before delivery.

Conclusion

The diagnosis of APL during pregnancy presents a challenge for both the patient and clinician, and a number of issues need to be considered. Whether the patient decides to continue or terminate the pregnancy, the
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treatment of APL should not be delayed. If the
diagnosis is made in the first trimester, pregnancy
termination should be discussed with the patient.
If the pregnancy is to continue, then the appropriate
chemotherapy regimen needs to be determined.
Frequent fetal monitoring, along with aggressive
management of potential APL-related complica-
tions, is necessary to allow for optimal maternal and fetal outcomes.

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