Acute Leukaemia During Pregnancy

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The association of leukaemia with pregnancy is very uncommon and not expected to occur in more than one in 75,000 pregnancies. Three pregnant patients with acute leukaemia were seen in our centre over a 5-year period. All three were seen during the second half of their pregnancy. Two patients had acute myelogenous and one had acute lymphoblastic leukaemia. Two patients received chemotherapy prior to delivery of the fetus while the third patient underwent Caesarean section prior to initiation of chemotherapy. During the course of hospitalization, there were two maternal deaths and one fetal death. No fetal malformations or anomalies were detected. The worldwide published experience on this subject has been reviewed and summarized.

The combination of acute leukaemia and pregnancy is very infrequent despite the fact that leukaemia is the second most common malignancy in women in their reproductive years.1 The association of leukaemia and pregnancy was first described by Virchow in 1845.2 More than 400 cases of leukaemia complicating pregnancy have been published since the original report of Virchow.3 Nevertheless, experience in managing leukaemia during pregnancy is still limited and a well-defined method for its treatment is lacking.

Fears about the teratogenic effects of cytotoxic drugs when given during pregnancy which originated from the older reports are still present among many haematologists and obstetricians despite the fact that some recent reports are quite reassuring as to the safety of these drugs especially during the second and third trimesters of pregnancy.3-6 Management of pregnant patients with acute leukaemia should be individualized but it is generally advisable to use the conventional anti-leukaemic regimens when decisions to initiate therapy have been made.

In this paper, we describe our own experience with acute leukaemia complicating pregnancy and review the published reports on this topic.

Patients and Methods
The records were reviewed of all patients with acute leukaemia admitted to the Haematology/Oncology Unit...
Table 1

<table>
<thead>
<tr>
<th>Patient no.</th>
<th>Age (years)</th>
<th>Stage of pregnancy (weeks)</th>
<th>Presentation</th>
<th>Bone marrow diagnosis</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>26</td>
<td>32</td>
<td>Septicaemia, (M4) AML</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>epistaxis diffuse pulmonary infiltrate</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>24</td>
<td>24</td>
<td>Leukaemic meningitis seizures</td>
<td>ALL</td>
</tr>
<tr>
<td>3</td>
<td>28</td>
<td>28</td>
<td>Fever; profound (M5a) AML weakness</td>
<td></td>
</tr>
</tbody>
</table>

AML = Acute myeloid leukaemia.
ALL = Acute lymphoblastic leukaemia.

at King Khalid University Hospital in Riyadh during the period January 1986 to December 1990. Among 90 patients with acute leukaemia admitted, three cases of acute leukaemia occurring during pregnancy were identified. We present here summaries of these three cases. In addition, an extensive review of the recent English literature on similar cases was carried out in order to make meaningful conclusions and recommendations.

Results
The details of the three cases of acute leukaemia complicating pregnancy are summarized in Tables 1 and 2. All three patients were managed in a reversed isolation setting, nursed with the standard anti-septic precautions and received prophylactic blood component therapy. Broad-spectrum antimicrobial coverage was also administered for proven or suspected infection.

Discussion
The exact incidence of acute leukaemia complicating pregnancy and the frequency of pregnancy occurring in patients with acute leukaemia are unknown. Recent estimates suggest that acute leukaemia is not expected to occur in more than one in 75,000–100,000 pregnancies which is essentially the same frequency at which acute leukaemia is expected to occur in non-pregnant women aged 15–45 years. Estimates of pregnancy occurring in patients with acute leukaemia are not available but with more patients kept alive with modern therapy, this frequency is expected to rise.

Experience in the management of pregnancy complicated by acute leukaemia is limited because of the relatively small number of cases reported. This is further complicated by the fact that most of the available literature covers only small series and individual case reports. This not only indicates the lack of a standard approach to the disease but rather, that those cases with unusual features and those with a successful outcome tend to be reported more than others.

A review of 71 newly diagnosed cases of acute leukaemia complicating pregnancy which have been reported in the English literature between 1975 and 1995 showed that 47 cases (66%) were myeloid and 24 cases (34%) were lymphoid in origin. Acute leukaemia appeared more frequently during the later stages of pregnancy. It was detected in 14 cases (20%) during the first trimester, in 27 cases (38%) during the second and in 30 cases (42%) during the third trimester.

Table 2

<table>
<thead>
<tr>
<th>Patient no.</th>
<th>Induction chemotherapy</th>
<th>Delivery</th>
<th>Fetus</th>
<th>Course</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Cytosine arabinoside 100 mg/m² per day for 7 days</td>
<td>Caesarean section prior to chemotherapy</td>
<td>Normal female weight 1875 g</td>
<td>Patient died on day 17 of treatment with respiratory failure</td>
</tr>
<tr>
<td></td>
<td>Daunorubicin 60 mg/m² per day for 3 days</td>
<td>Caesarean section after achieving complete remission</td>
<td>Normal male weight 1270 g</td>
<td>Lost follow-up after 4 months</td>
</tr>
<tr>
<td>2</td>
<td>Cytosine arabinoside 50 mg intrathecally</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Vincristine 2 mg weekly × 6 weeks</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Prednisone 100 mg/day for 6 weeks</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>2.1 Grays cranial radiation delivered over 7 fractions</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>Same treatment as No. 1</td>
<td>Stillbirth</td>
<td>Dead but no congenital anomalies</td>
<td>Patient died on day 19 with progressive pneumonia</td>
</tr>
</tbody>
</table>

*This was given every 2 days till blast cells disappeared from CSF.

*The section was performed for pure obstetrical indications.
Available data suggest that pregnant patients with acute leukaemia are expected to achieve a complete remission rate comparable with that achieved in non-pregnant patients. A complete remission rate of 77% and 76% has been reported in pregnant patients with AML and ALL respectively. This is essentially similar to the remission rate reported in non-pregnant patients with the same disease. Data is limited, however, regarding the remission duration and the overall survival of complete remitters essentially because of incomplete follow-up information, small number of patients in individual series and the wide variety of post-remission treatment regimens used.

A major problem in pregnant patients with leukaemia is whether pregnancy or birth have any influence on the course of the disease. Pregnancy was suggested to be a poor prognostic factor in ALL. This, however, did not gain support from the published literature and it is generally felt now that pregnancy does not alter the course of the disease. An opposing view in the literature indicates that interruption of pregnancy may actually worsen the course of leukaemia, probably because of the sudden drop in the steroid hormone levels produced during pregnancy. For this reason some authors advised the administration of corticosteroids in the final days of pregnancy and the early postpartum period to offset this physiologic reduction.

The use of cytotoxic drugs in pregnant women with acute leukaemia has always been surrounded with fear and apprehension because of the possible teratogenicity of these drugs. The available data suggest that single and combination chemotherapy can be administered during the second and third trimester of pregnancy with very low-risk of teratogenicity. Some controversy still exists regarding the safety of using these agents during the first trimester of pregnancy. The older reports suggest that cytotoxic drugs given during the first trimester had been associated with a significant incidence of fetal malformation and increased frequency of early spontaneous abortion.

Some recent reports, however, have found that the use of these drugs during the first trimester has not necessarily been associated with excessive risk to the fetus not only prior, at, or immediately after birth but also in prolonged follow-up periods extending in some reports for more than 20 years. Thus until this controversy is resolved, physicians are advised to individualize their management plans according to patients' conditions and circumstances. In general, cytotoxic drugs should be avoided or delayed until the second trimester of pregnancy if this is possible. If it is not, the conventional treatment should be given with caution. The latter includes the avoidance of folate antagonists especially methotrexate because of the relatively high incidence of congenital malformations associated with its use during pregnancy. Fortunately, at present, methotrexate is not part of any conventional antileukaemic induction regimen. Other agents should be used according to established chemotherapeutic regimens as data on the pharmacokinetics of antineoplastic agents in pregnancy is lacking. It should be emphasized here that problems other than teratogenicity should also be expected to occur with the use of antileukaemic agents. These may include low-birth weights, intrauterine growth retardation, spontaneous abortions and premature births. The role played by the leukaemia itself in producing these problems is unknown.

The role of elective Caesarean sections performed prior to the administration of chemotherapy when fetal viability has been confirmed is not well-defined. The authors feel that 'prophylactic' sections may not be of major impact in improving the fetal welfare since those patients in whom elective sections can be safely carried out are the ones in whom maternal and fetal complications are expected to be minimal. Two of our patients underwent Caesarean sections (Case nos 1 and 2) for different indications. Patient no. 1 had progressive respiratory failure and it was felt that relieving the pressure on the diaphragm by the gravid uterus might have stabilized her respiratory decompensation. Patient no. 2 underwent Caesarean section after she had been treated with chemotherapy and was in complete remission. The indication for the operation was the patient's expected intolerance of vaginal delivery by running into respiratory difficulties due to her tracheal stenosis.

Delivery should generally be planned when the maternal counts are optimal. Bleeding during delivery may occur in up to 25% of patients and is usually mild but continuous and mainly due to thrombocytopenia although factors such as hypofibrinogenaemia or disseminated intravascular coagulation may play a role. Thus, supportive therapy with platelet concentrates with or without clotting factor replacement is expected to reduce the incidence of bleeding complications. Septic complications are major causes of morbidity and mortality in leukaemic patients, but wound infection at the site of episiotomy, surgical scars or vaginal tears may add to the pre-existing risk in leukaemic pregnant patients at the time of delivery.

The infant should undergo haematological evaluation and examination for congenital malformations and organ dysfunction followed by short- and long-term follow-up evaluations to detect any potential but delayed complication. Breast feeding is generally contraindicated when the mother is receiving chemotherapy. This is particularly
true for agents which are known to be excreted into the milk such as doxorubicin,\textsuperscript{25} cyclophosphamide\textsuperscript{26} and methotrexate.\textsuperscript{27}

Our limited number of patients is an obstacle to making experience-based recommendations, a problem that is not unique to our centre but is shared by most other centres dealing with leukaemias. Thus many questions as to the best approach to pregnant patients with acute leukaemia will remain unanswered until a large number of patients has been studied. Due to the rarity of such an association, experience is unlikely to accumulate in any one centre or perhaps in any one country. A national and international registry, although it would be practically difficult, would seem to be the only potentially promising solution for this problem.

References
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\textsuperscript{17}Hoelzer D, Gale RP. Acute lymphoblastic leukemia in adults: Recent progress, future directions. \textit{Semin Hematol} 1987; 24: 27–39.
\textsuperscript{26}Wiernik PH, Duncan JH. Cyclophosphamide in human milk. \textit{Lancet} 1971; 1: 912.