Fetal Effects of Coumadin Administered During Pregnancy

By J. Hirsh, J. F. Cade and A. S. Gallus

The safest and most practical method of administering long-term anticoagulants in pregnancy is uncertain because treatment of the mother with vitamin K antagonists may be complicated by hemorrhage in the fetus. The effects on the fetus of giving coumadin in pregnancy was evaluated in rabbits. When coumadin was given from early pregnancy until term, all of the fetuses were stillborn with widespread hemorrhages. However, the fetuses were born alive and without hemorrhage when (1) coumadin was stopped 4–5 days before delivery, at which time the level of coagulation factors had almost returned to normal and (2) when delivery was performed by cesarean section at a time when the fetal coagulation defect was severe. It is suggested that the risk of fetal hemorrhage is high only when fetuses with a severe coagulation defect are exposed to the trauma of delivery.

The use of anticoagulants in pregnancy presents a special problem because treatment may be complicated by fetal hemorrhage. Two groups of anticoagulant drugs are available, heparin and the vitamin K antagonists. Heparin is thought to be the more effective and is safer for the fetus because it does not cross the placenta, but as it must be given parenterally, its long term use is inconvenient. The vitamin K antagonists on the other hand have been shown in experimental animals to cross the placenta and to cause fetal hemorrhage. They have therefore been considered to be contraindicated during pregnancy, although this view has recently been questioned. Review of the experimental and clinical evidence suggested to us and to Bloomfield and Rubinstein that an increased risk of fetal hemorrhage may exist only when the mother is given oral anticoagulants near term. Nevertheless, the evidence is inconclusive and the safest and most effective approach to anticoagulant treatment in pregnancy remains uncertain.

We have therefore re-examined the effects of giving vitamin K antagonists to pregnant rabbits with the particular aim of determining the causal factors responsible for fetal and neonatal hemorrhage.

Materials and Methods

Coagulation Tests

The following coagulation tests were performed on maternal and fetal rabbit blood: the prothrombin time (P.T.) and assays of factors II, V, VII and X complex, VIII, X and fibrin-
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ogen. The methods were as previously described\textsuperscript{13} except that the blood was diluted 1:10 in sodium citrate solution (0.38 Gm. per cent in normal saline) so that a comprehensive coagulation assessment could be made on the small samples of blood available from each fetus.

**Blood Sampling**

Adult rabbits were bled from the lateral marginal vein of the warmed ear using a 23 gauge needle and a plastic syringe containing 0.38 Gm. per cent sodium citrate. Fetal blood was taken at cesarean section from the exposed umbilical vein using a 23 gauge needle and a plastic tuberculin syringe containing 0.38 Gm. per cent sodium citrate. Neonatal blood was taken by cardiac puncture from the unanesthetized animal using the same procedure. Platelet-poor plasma was prepared from the diluted blood by centrifuging at 2000 \( \times \) g. for 10 minutes at 4\(^\circ\) C and the tests were performed on the same day.

**Experimental Procedure**

Standard curves for the prothrombin time and individual factor assays were constructed using pooled plasma prepared from adult rabbit blood diluted in sodium citrate solution, as above. The studies were performed on four groups of pregnant rabbits and their fetuses.

*Group 1.* Tests were performed on untreated mothers, their fetuses and newborn kittens. Fetuses (gestation age 25–29 days) were tested at cesarean section and the kittens (30–32 days) within 6 hours of delivery.

*Group 2.* Pregnant rabbits were given coumadin from approximately 1 week after conception until term. The maternal prothrombin time was measured every second day and was maintained between approximately 10 and 40 per cent of normal levels by giving coumadin, 1–3 mg. per kg. of body weight, by intramuscular injection, every second or third day. These rabbits were allowed to come into labor spontaneously and their fetuses were examined.

*Group 3.* Pregnant rabbits were treated in the same way as those in Group 2 but cesarean section was performed 1 day before the anticipated day of labor (29–30 days gestation). The fetuses were examined and fetal blood was taken at operation from the umbilical vein for coagulation factor assays.

*Group 4.* Pregnant rabbits were treated with coumadin as above with the exception that treatment with coumadin was stopped 4–5 days before term. These rabbits were allowed to deliver vaginally, the kittens were examined and coagulation tests were performed on mothers and kittens within 6 hours of delivery.

**Results**

*Group 1.* The results of coagulation tests performed on control fetuses and neonates are shown in Table 1. There was little variation in the levels of coagulation factors assayed over the range of 25–32 days gestation.

*Group 2.* (Table 2). The five pregnant rabbits given coumadin from approximately 1 week after conception until term gave birth to 26 stillborn fetuses,

**Table 1.—Group I: Coagulation Tests on Fetuses from Untreated Mothers**

<table>
<thead>
<tr>
<th>Mothers</th>
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</thead>
<tbody>
<tr>
<td>No.</td>
<td>P.T. Per Cent</td>
<td>No.</td>
<td>Gestation in Days</td>
<td>P.T. Per Cent</td>
<td>II</td>
<td>V</td>
</tr>
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<td>---------</td>
<td>-------------</td>
<td>---------</td>
<td>--------------------</td>
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<td>---</td>
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</tr>
<tr>
<td>6</td>
<td>105</td>
<td>33*</td>
<td>25–32</td>
<td>75</td>
<td>80</td>
<td>66</td>
</tr>
<tr>
<td></td>
<td>(10.5)</td>
<td></td>
<td></td>
<td>(20.2)</td>
<td>(15.4)</td>
<td>(25.1)</td>
</tr>
</tbody>
</table>

* Twenty-seven premature fetuses tested at cesarean section and six mature neonates tested after spontaneous delivery.

P.T., Prothrombin time.

Values are means with standard deviations in parentheses.
all with widespread subcutaneous hemorrhage. The mean maternal prothrombin time at delivery was 20 per cent.

**Group 3.** (Table 2.) The seven pregnant rabbits given coumadin from approximately 1 week after conception until cesarean section (performed at 29–30 days gestation), had 40 fetuses, all alive and without hemorrhages. The mean maternal prothrombin time (21%) was essentially the same as in group 2. The mean fetal prothrombin time was less than 5 per cent and there was a marked depression of the three vitamin K-dependent coagulation factors assayed.

**Group 4.** (Table 2). Five pregnant rabbits were given coumadin as in Group 2, except that the drug was stopped 4–5 days before term. There were 30 neonates, all born alive and without hemorrhages. The mean maternal prothrombin time at delivery was 83 per cent and the mean prothrombin time in the neonates was 62 per cent. The level of vitamin K-dependent clotting factors were slightly lower than in the controls.

**Discussion**

Early experiments by Quick and Kraus, Perlow and Singer demonstrated a high incidence of fetal hemorrhage and death following administration of coumarins to pregnant dogs and rabbits. In both of these studies, the fetuses were delivered at a time when their coagulation system was severely impaired because large doses of the drugs were given until term. The results of the present study confirm these reports, but in addition suggest that hemorrhage occurs only when fetuses with a severely impaired coagulation system are exposed to the trauma of delivery. Thus, when the pregnant rabbits were given coumadin until term, all the fetuses that delivered spontaneously were stillborn with widespread hemorrhage, but those delivered by cesarean section were alive and without hemorrhage, even though their vitamin K-dependent coagulation factors were very low. Furthermore, when the administration of coumadin to the mother was stopped 4–5 days before term so that the levels of fetal clotting factors had returned to near normal before delivery, all the fetuses were born alive and without hemorrhage.

Although the results of animal studies must be interpreted with caution the proposal that an increased incidence of fetal hemorrhage occurs only when treatment with the vitamin K antagonists is continued until term is in keeping with a number of clinical observations. Von Runge and Hartert gave coumarins to 12 women before they underwent legal abortion and did not find evidence of fetal hemorrhage. In addition, detailed examination of the cases of antepartum thrombophlebitis that were reviewed by Villasanta in 1965 showed that of 10 patients still receiving oral anticoagulants at the 40th week of gestation, there were five instances of perinatal hemorrhage, but that in the 47 cases given oral anticoagulants at an earlier stage of pregnancy and stopped before term, only one of 13 fetal deaths was clearly due to hemorrhage.

The possibility that the vitamin K antagonists produce fetal damage by means other than hemorrhage was not evaluated in the present study, but requires serious consideration. Kraus and associates found a number of poorly
Table 2—Coagulation Tests and Perinatal Fetal Hemorrhage and Mortality in Coumadin-Treated Pregnant Rabbits and Their Neonates

<table>
<thead>
<tr>
<th>Group</th>
<th>Mothers</th>
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<th>Neonates</th>
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<th></th>
<th></th>
<th></th>
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<th></th>
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<th></th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No.</td>
<td>P.T.</td>
<td>No.</td>
<td>P.T.</td>
<td>Fibrinogen</td>
<td>II</td>
<td>V</td>
<td>VII and X</td>
<td>X</td>
<td></td>
<td></td>
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<td></td>
<td>Per Cent</td>
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<td>Per Cent</td>
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<td></td>
<td></td>
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</tr>
<tr>
<td>2. Coumadin given until delivery</td>
<td>5</td>
<td>20 (10.2)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>All stillborn with multiple subcutaneous hemorrhages</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>3. Coumadin given until cesarean section</td>
<td>7</td>
<td>21 (10.2)</td>
<td>40</td>
<td>&lt; 5</td>
<td>300</td>
<td>&lt; 1</td>
<td>51</td>
<td>3</td>
<td>2</td>
<td>All alive without hemorrhages</td>
<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>4. Coumadin stopped 4–5 days before term</td>
<td>5</td>
<td>83 (9.6)</td>
<td>30</td>
<td>62</td>
<td>367</td>
<td>45</td>
<td>56</td>
<td>55</td>
<td>48</td>
<td>All born alive and without hemorrhages</td>
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</tbody>
</table>

P.T., prothrombin time.
The values are means with standard deviations in parentheses.
developed fetuses in pregnant rabbits given coumarins, and nasal bone malformation has been reported in two cases in humans when mothers were given coumadin in the first 2 months of pregnancy. In addition, there are the reports referred to above of nonhemorrhagic fetal death occurring in association with the administration of vitamin K antagonists in pregnancy. However, the true importance of these sporadic reports is uncertain and can really only be determined by systematic investigation.

REFERENCES

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