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MATERNAL-FETAL TRANSFER OF IRON IN SHEEP

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Introduction:

Our interest in the maternal-fetal transfer of iron arises from the desire to assess the radiation dose to the human fetus when the mother is given radioactive ^{59}Fe . During the late 1940's, iron metabolism studies with ^{59}Fe were performed in approximately 800 pregnant women at Vanderbilt University. During the middle 1960's, a follow-up study on the children resulting from these and control pregnancies found three malignancies among the exposed children while none were found among the control or non-exposed group. In order to place this observed tumor incidence in proper perspective, the radiation dose received by the exposed children needs to be evaluated. For this evaluation, information is needed on the maternal-fetal transport of iron and the distribution of the transported iron within the fetus. We have obtained this information during the early stages of pregnancy, 8 to 22 weeks, from studies on pregnant women receiving therapeutic abortions, but this means of investigation does not provide information on the late stages in pregnancy. Also, because of experimental difficulties, the therapeutic abortion studies provide information at only one point in time, about eighteen hours after administration of the iron tracer. In order to obtain information later in pregnancy and on iron transport timing, we have conducted studies in pregnant sheep which this paper describes.

Methods:

The maternal-fetal transfer of iron was studied in six ewes who were from 130 to 135 days of gestation. Several days prior to beginning the study, catheters were implanted within the maternal and fetal circulatory systems. Approximately 30 μCi of ^{59}Fe were injected into the ewe and at the same time about 200 μCi of ^{55}Fe were given to the fetus. Both the iron isotopes injected were in the ferrous citrate form and essentially carrier free. During each study, about forty samples of maternal and fetal blood were taken with frequent sampling during the first day. The fetuses were removed by Cesarean section at from 70 to 120 hours after administration of the iron tracer. Both the ewe and the lambs were sacrificed shortly after the Cesarean section and samples of maternal and fetal placenta, liver, and spleen were obtained. A wet weight was determined for all samples.

The ^{55}Fe and ^{59}Fe activities in the blood and organ samples were quantitated by liquid scintillation counting. The stable iron concentration of the maternal and fetal organ samples was measured using the atomic absorption method.

Results:

The amount of fetal-administered iron tracer transported to the ewe was undetectable. This agrees with information in the literature for other mammals. That is, iron transport across the placenta is unidirectional with very little or no transport to the maternal unit from the fetus. Also we found no detectable transfer of iron from one fetus to another when more than one fetus was present in utero.

From the early and closely spaced blood samples, the maternal and fetal plasma iron clearances were determined. Table I presents the average maternal and fetal plasma iron clearance half-times. The maternal half-time ranged from 100 to 180 minutes with a mean of 151 minutes. This agrees with the plasma iron clearance half-time reported in the literature for the adult male sheep. One would think that due to iron demands by the fetus, the plasma iron clearance rate would be increased in pregnancy but this does not appear to be the case for late gestational stage ewes. The average fetal plasma iron clearance half-time was 149 minutes which is essentially the same as for the ewes. For the near term, fetal goat in utero, a much faster plasma iron clearance rate with a mean half-time of 22 minutes has been reported as compared to this value of 149 minutes for the fetal sheep.

Figure I is a graph of the amount of ^{55}Fe or fetal-administered iron tracer incorporated into fetal blood versus time after administration. The x-axis plots the time in hours while the y-axis is the incorporation of the iron tracer plotted logarithmically in normalized units. The data from each fetus have been normalized to one at the time of 72 hours after injection. At the time of 72 hours, maximum incorporation of the fetal tracer iron into fetal blood was found for all fetuses.

Figure II presents a graph of the amount of ^{59}Fe or maternal-administered tracer incorporated into maternal blood versus time after administration. For each sheep the maternal and fetal administrations were done simultaneously. Again, the axes are the same as for the previous graph and the data from each ewe were normalized to one at the time of seventy-two hours. As can be seen from this graph, the time for maximum tracer incorporation into blood is later for the ewe

than for the fetus, about 100 hours for the ewe as compared to about 72 hours for the fetus.

Figure III shows the incorporation of maternal-injected ^{59}Fe tracer into fetal blood versus time after maternal administration. The coordinates and units are the same in this graph as for the previous two graphs with the incorporation data for each fetus normalized to one at the time of seventy-two hours. In this case, the incorporation of the maternal iron tracer into fetal blood is a combination of the transport of the tracer to the fetus plus the tagging of the fetal red blood cells with the ^{59}Fe . The maximum incorporation time of the maternal-introduced tracer into fetal blood is about 96 hours. This is about 24 hours longer than the time of 72 hours for the maximum incorporation of the fetus administered ^{55}Fe tracer.

Table II presents the relative stable iron concentration of maternal and fetal placenta, liver and spleen. The stable iron concentrations for the two sides of the placenta were essentially the same and the data presented are expressed as a multiple thereof. The fetal liver stable iron concentration was over eight times higher than the placenta while the maternal liver was only twice as high. This reflects the large red cell production activity of the fetal liver. For the maternal spleen, however, the stable iron concentration was over 13 times higher than the placenta while the fetal spleen was only about twice as high. The lower iron concentration in the fetal spleen reflects the small amount of erythrocyte sequestration in the fetal spleen because of its short life time relative to the ewe.

Table IV shows the transport to the total fetus, fetal liver and fetal spleen of the ^{59}Fe tracer given intravenously to the ewe. Only

about one-half of one percent of the tracer given the ewe appeared in the fetus. The magnitude of the iron transport to the fetus is much lower for the sheep than for some other mammals such as mice, rabbits, and swine. However, the distribution of the transferred iron within the fetal sheep, about one-fourth in the fetal liver, is similar to what has been found for other mammals. The consistently high stable iron concentration and radioactive iron incorporation for the fetal liver point to this organ as the major site of fetal red cell production.

Figure V is a plot of the transport to fetal blood of the maternal-injected ^{59}Fe tracer versus time after injection in hours. As is shown in this slide, maximum fetal blood transport does not occur until about 120 hours after injection. The percent of the maternal-given tracer is about six times higher at 120 hours than it is at 18 hours post injection. The 18-hour time after administration of the maternal tracer is important to us because it is the timing point of our human data from therapeutic abortions. If this six-fold increase of iron transport between 18 and 120 hours found in the fetal sheep is also true for the human fetus, then the self-dose estimates to the early stage human fetus from ^{59}Fe we have made would be low by a factor of six. Since the self-fetal dose is only a part of the total fetal dose, then the previously reported radiation dose of 35-40 Rad/mCi to the early stage human fetus would be increased by a factor of three to about 120 Rad/mCi of ^{59}Fe injected intravenously into the mother. However, because of the long plasma clearance half-times and the lower maternal-fetal iron transport found for the fetal sheep, we believe that the time of 120 hours for maximum iron transport may not be applicable to other fetal mammals, including the human fetus.

Table V presents the estimated radiation dose to the 34-36 week human fetus calculated from the sheep maternal-fetal transport data measured in this study. The sheep data were modified using previously reported data for both sheep and man. The estimated radiation doses to the human fetal spleen of 71.6 rads per mCi and fetal liver of 66.7 rads per mCi are about three times the total fetal dose of 25.1 rads per mCi.

Summary:

In summary, we have measured the bi-directional maternal-fetal transport and the fetal utilization of iron for six sheep late in pregnancy. The placental transfer and fetal tissue utilization of iron are lower for sheep than for other mammals. Only one-half of one percent of the iron tracer given the ewe appeared in the fetus. There was no detectable iron transport to the ewe from the fetus. A significant time delay between the incorporation of the fetal and administered iron tracers into fetal blood was found. An investigation of this time delay may provide a better understanding of placental physiology for iron transport.

Using the modified sheep data, the total fetal radiation dose to the 34-36 week human fetus was estimated to be 25.1 rads per mCi. This is lower than the total fetal radiation dose of 35-40 rads per mCi for the 8-22 weeks human fetus that we estimated from our therapeutic abortions studies. The fetal liver dose which we estimated to be around 400 rads per mCi for the 8-22 week human fetus is only about one-sixth as much for the 34-36 week human fetus. The observed malignancies in the children exposed to ⁵⁹Fe in utero were only found in those exposed early in pregnancy. The lack of observed malignancies in the children exposed in the later gestational stages is consistent with the lower radiation doses estimated for these children.

TABLE I
PLASMA IRON CLEARANCE FOR SHEEP

	Average Clearance Half-Time (min)	Clearance Half-time Range (min)
Ewe (^{59}Fe)	151	100-180
Fetus (^{55}Fe)	149	115-172

TABLE II

RELATIVE STABLE IRON CONCENTRATION

Organ	Maternal	Fetal
Placenta	1.00	1.00
Liver	2.06	8.30
Spleen	13.5	2.06

TABLE IV

^{59}Fe TRANSPORT TO FETUS
IN PERCENT OF MATERNAL I.V. DOSE

Organ	Average Uptake (%)
Total Fetus	.511
Fetal Liver	.124
Fetal Spleen	.00101

TABLE V

RADIATION DOSE TO 34-36 WK FETUS AND FETAL
ORGANS FROM ^{59}Fe ADMINISTERED I.V. TO MOTHER

	Rad/mCi
Total Fetus	25.1
Fetal Liver	66.7
Fetal Spleen	71.6

FIGURE I
 ^{55}Fe INCORPORATED INTO FETAL BLOOD
VERSUS TIME AFTER FETAL I.V. ADMINISTRATION

FIGURE II
 ^{59}Fe INCORPORATED INTO MATERNAL BLOOD
VERSUS TIME AFTER MATERNAL I.V. ADMINISTRATION

FIGURE III

^{59}Fe INCORPORATED INTO FETAL BLOOD
VERSUS TIME AFTER MATERNAL I.V. ADMINISTRATION

FIGURE V
 ^{59}Fe TRANSPORT TO FETAL BLOOD
VERSUS TIME AFTER MATERNAL I.V. ADMINISTRATION