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Glucose homeostasis in human fetuses

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The blood glucose concentrations of 101 fetomaternal pairs of different gestational ages were studied. The glucose concentration was highest in fetal heart blood, followed by umbilical vein, cord and arterial blood. The maternal blood glucose obtained during operation was always higher than the fasting maternal. The different anesthetics had different effects on both fetal and maternal blood glucose level; anesthetic stress which caused rise in maternal blood glucose level may or may not be reflected in fetal heart blood. Effect of infusion of different fluids like normal saline 5 per cent dextrose or Ringer's lactate administered to mother is not clear. Furthermore, our data suggest that arteriovenous difference was 0·5 to 1 mmole/litre, so the finding is in support of the view, that facilitated diffusion is occurring across the placenta, and high fetal heart blood glucose concentration in certain cases is due to separate regulatory events.

Key words : Gluconeogenesis; glucose homeostasis human fetus; glycogenolysis.

There is a difference in glucose homeostasis between an adult and a fetus. Although the fetus is independent of the exigencies of supply from the environment in as much as the mother provides it with a steady input, there are variations in the level of supply. For example, when the maternal blood glucose level rises after the meals, the increased maternal sugar concentration is reflected with an increased sugar concentration in the fetal blood. It is true that the fetus is spared the stress of hypoglycemia due to maternal adjustments, it has to contend with increased blood sugar concentrations. Therefore, to study the regulation of the fetal blood glucose concentration is of paramount importance. It is more so, in case of human fetuses because of numerous instances of prematurity and intrauterine growth retardation in this species.

Carbohydrate metabolism and regulation of blood glucose in fetus has been reviewed by Ballard.[1] The blood glucose level in human fetuses of mid-gestation and at term were studied by a number of workers.[2-4] The blood from umbilical cord, vein or superior sagital sinus have been utilized for the purpose.[2-7] Furthermore, because of relative non-availability of human fetuses the number of fetuses studied in each series has been rather limited. Most of the previous informations about the glucose metabolism in fetal development were based on the studies on other mammalian species like sheep, pig, rat and guineapig, but in those species a totally different developmental profile exists. In the present report we are presenting data on 101 maternofetal pairs of different gestation periods. The glucose concentration in the maternal blood were

compared to the glucose concentration in different body fluids like cord blood, heart blood, umbilical arterial and venous blood of the conceptus.

Material and Methods

These studies were conducted in the Medical Termination of Pregnancy Clinics of SSKM hospital, and Department of Biochemistry attached to the Institute of Post Graduate Medical Education and Research. Human fetuses were obtained from normal healthy mothers undergoing hysterotomy and ligation. The authors had no say in the selection and operation of the subjects, which were carried out by the Professor of Obstetrics of the Institute. The project was cleared by the ethical subcommittee of the Institute. Maternal blood was taken in heparinized syringes from the dorsal cubital vein at 6 a.m. (i.e. on empty stomach) on the day of operation and immediately before the fetus was taken out of the uterus. Within five minutes after their separation from the mothers womb, the fetuses were utilized. Attempts were made to take out the entire conceptus within the amniotic sac wherever possible. Fetal blood specimens were drawn in heparinized syringes from umbilical vein, artery, cord and from heart (by cardiac puncture of right atrium). Three modes of anesthesia were used. Thiopentone induction with either suxamethonium or gallamine followed by oxygen, nitrous oxide and ether or fluothane was used in one series. Epidural anesthesia with xylocaine was used in another and open ether anesthesia was used in the third series. The mothers were infused during operation with either 5 per cent dextrose saline or normal saline or Ringer's lactate solution at the rate of 2 ml per minute. Glucose was estimated by glucose oxidase method.[8]

Results

Table I shows the glucose concentration in blood obtained from umbilical artery, vein, cord and heart in fetuses and compares them with the maternal fasting blood glucose concentration and concentration during operation. The concentration in the heart blood was highest followed by umbilical vein, cord and arterial blood in decreasing order. The difference between the fetal heart blood glucose concentration and umbilical venous blood glucose concentration is statistically significant ($0{\cdot}001 < p < 0{\cdot}05$). The glucose concentration of umbilical venous blood was about 1·0 m*M* higher than the umbilical arterial with umbilical cord blood concentration in between. The correlation between the umbilical arterial and umbilical venous glucose concentration is high ($r = 0{\cdot}88$) and the venous concentration was always found to be higher than arterial blood glucose concentration. It is apparent that maternal fasting glucose concentration was higher than the umbilical arterial and venous concentration, the difference is statistically significant between maternal fasting and umbilical arterial ($p < 0{\cdot}001$), but the difference between umbilical venous blood glucose concentration and fasting maternal blood glucose concentration was found to be insignificant. However, when we compare the glucose concentration of heart blood with that of the fasting maternal blood it appears that the glucose concentration of fetal heart blood was higher than that of fasting maternal and the difference is again statistically significant ($0{\cdot}001 < p < 0{\cdot}05$). The glucose concentration of the

maternal blood during the operation of hysterotomy and ligation was always higher than that of glucose concentration of the fetus, no matter whether the fetal blood was from umbilical vein, artery or cord or from fetal heart.

In most cases, only the fetal heart blood was available for study. Glucose concentration of such blood was compared with the concentration of maternal blood during fasting and during operation of hysterotomy and ligation. Table II represents the results. The glucose concentration of fetal heart blood was higher than the maternal fasting blood glucose concentration. The difference was statistically significant at lower than 0·01 level ($p<0·01$). However, the fetal heart blood glucose concentration was lower than the maternal blood glucose concentration during operation. The difference was again statistically significant ($p<0·001$).

Table I. Human fetal and maternal blood glucose concentration (in m moles/l.)

Source of fetal blood	Fetal blood glucose concentration	Maternal blood glucose concentration	
		During fasting	During operation
Umbilical artery	(14) 2·220±0·273*	(11) 3·635±0·217	(14) 6·648±0·640
Umbilical vein	(16) 3·227±0·302	(12) 3·726±0·259	(16) 6·303±0·615
Umbilical cord	(29) 3·105±0·224	(23) 3·159±0·135	(29) 6·176±0·499
Fetal heart	(37) 4·169±0·252	(30) 3·370±0·142	(37) 6·494±0·431

Figures in parentheses represents number of samples. *Mean±SEM

Table II. Human fetal heart blood glucose concentration and their corresponding maternal blood glucose concentration (in m mole/l)

	Maternal blood glucose concentration	Fetal heart blood glucose concentration	t value	p value
During fastening	3·843±0·132* (52)	4·745±0·254 (52)	$t_{102}=3·150$	$>0·001$
During operation	6·619±0·279 (101)	5·258±0·220 (101)	$t_{200}=3·825$	$<0·001$

Figures in parentheses represents number of samples. *Mean±SEM

In the present series of investigation there were 30 pair of feto-maternal glucose concentration in 13-16, 50 in 17-20 and 20 in 20-24 weeks of gestation. The correlation between fetal heart blood glucose and maternal blood glucose is positive in all the age groups. The results are shown in Table III. The correlation is statistically significant in 17-20 weeks period of gestation ($p<0{\cdot}001$). In 13-16 and 21-24 weeks period of gestation, the correlation is not statistically significant ($p>0{\cdot}05$).

Since the maternal blood glucose concentration is in equilibrium with umbilical venous concentration and since fetal blood glucose concentration was found lower than, equal to or higher than maternal concentration it was considered of interest to study whether the fluctuation observed was due to a corresponding variation of maternal blood glucose as a result of being infused during the operation. Table IV gives the results. When Ringer's lactate solution being infused maternal blood glucose during operation was found to increase by 34 per cent above the fasting level ($p<0{\cdot}05$), when dextrose saline (5%) being infused the maternal blood glucose during operation was found to increase by 45 per cent

Table III. Correlation between fetal blood glucose concentration and maternal blood glucose concentration at different period of gestation

Age group	Period of gestation (in weeks)	No of sample studied	Correlation co-efficient (♂ FBS & MBS)	t test	p value
B	13-16	30	+0·201	5·22	>0·05
C	17-20	50	+0·420	2·09	<0·001
D	21-24	20	+0·330	5·96	>0·05

Table IV. Effect of infusion on human fetal and maternal blood glucose concentration (in m moles/l)

Type of infusion	No. of cases	Maternal blood glucose concentration		Fetal heart blood glucose concentration
		During fasting	During operation	
RL	25	4·04±0·63	5·58±0·46	4·97±0·63
DS	37	4·55±0·27	6·65±0·50	6·04±0·54
NS	12	—	4·53±0·55	5·25±0·55

R.L.=Ringer's lactate solution. DS=5% dextrose saline solution. NS=Normal saline solution.

above the fasting level. The rise in blood glucose level in both the groups are statistically significant. The fetal blood glucose concentration in these two groups were lower than the corresponding maternal during operation, but higher than the maternal blood glucose level during fasting. Moreover difference between the fetal glucose level and maternal glucose level both, during fasting and operation was statistically insignificant. However, when normal saline was being infused the fetal heart blood glucose concentration was higher during operation ($p<0\cdot05$). Unfortunately, the fasting maternal concentration was not done in this series, had it been done the difference might have been still more marked.

Administration of anesthesia to the mother during operation may produce alterations in the energy utilization in the fetus. Three modes of anesthesia were used. Results are shown in Table V When general anesthesia was used, maternal blood glucose increased 53 per cent over the fasting level ($0\cdot001<p<0\cdot01$), when epidural anesthesia was used the maternal blood glucose during operation increased by 65 per cent over the fasting level ($p<0\cdot05$), the increase is 152 per cent above the fasting level when open ether anesthesia was used. The fetal heart blood glucose was lower than the maternal blood glucose during operation but higher than the fasting maternal concentration in three groups. All the differences between fetal and maternal blood glucose concentration was not statistically significant. Thus open ether anesthesia produced the highest increase of maternal blood glucose during operation and in this series fetal blood glucose concentration was always lower from the maternal blood glucose during operation and was either equal to or slightly higher than the maternal fasting level.

The variation between duplicate estimations of blood sugar did not exceed ±5 per cent and recovery of added sugar by the method was between 93 per cent and 106 per cent.

Table V. Effect of different modes of anesthesia on glucose concentration of maternal and fetal blood (in m moles/l)

Type of anesthesia	No. of cases	Maternal blood glucose concentration		Fetal blood glucose concentration from the heart
		During fasting	During operation	
General anesthesia with (thiopentone induction with either suxamethionium or gallamine)	27	4·280±0·241*	6·570±0·502	5·000±0·527
Epidural with xylocaine	9	5·180±0·522	8·550±1·130	7·277±1·040
Open ether	4	3·890	9·830	4·220

*Mean±SEM

Discussion

In adults there is very little arteriovenous difference in glucose concentration in the post absorptive state, using capillary blood as representative of arterial blood.[9] During absorption of glucose, in glucose tolerance test the arterial blood glucose concentration is higher than the venous. The blood glucose concentration in the fetus was highest in heart blood. It was even higher than umbilical venous ($p<0\cdot05$). The arteriovenous concentration difference in the umbilical cord was between 0·5 and 1·0 m mole/litre. The difference is similar to that found in newborn human and midterm human fetuses.[2-4,10] The umbilical venoarterial glucose concentration difference is to be expected as the umbilical aretrial blood during its transit through the placenta acquired the higher concentration of blood glucose from the maternal circulation. But the concentration of blood glucose in the heart blood being higher than that in the umbilical venous blood is something of a puzzle. The umbilical venous blood during its sojourn from the placenta to the heart takes two routes, one through ductus venous which empties directly into the inferior vena cava and the other through numerous smaller openings into the fetal hepatic circulation, which ultimately open into the inferior vena cava through hepatic veins.[11] The liver therefore must have contributed some glucose to the blood when it was traversing through the organ.

Most of the studies on the maternofetal blood glucose concentration have reported blood glucose concentration in the fetus to be lower than in the mother.[2,3,12] However there are some studies, which show no difference in the maternal peripheral venous and umbilical venous concentration.[13,14] It stands to reason that in order to supply glucose continously to the fetus through the placental circulation the gradient must be from mother to fetus, since glucose transport through the placenta is thought to be of the facilitated diffusion type.[15,16] This is also borne out by our studies where plasma glucose concentration in the umbilical artery was lower than the fasting maternal venous concentration by about 1·0 m mole/litre.

The peripheral venous concentration of glucose in the mother and the concentration in the uterine veins have been shown to be identical[3] so there can be no difficulty in assuming that the diffusion follows the concentration gradient. However, the concentration of glucose in fetal heart blood being greater than the umbilical venous and sometimes higher than the maternal fasting blood sugar concentration can be misinterpreted as not following a diffusion gradient. But this is an artefactual situation because there may be some contribution of glucose by the fetal liver in raising the heart sugar concentration. Furthermore, there is a temporary rise of maternal blood glucose during the operation of hysterotomy. Although increased diffusion of sugar under such circumstances may be minimal due to lowered placental metabolism and some as yet undetermined effects on fetal metabolism and saturability of the carriers in the placental transport, the fetal sugar concentration in the umbilical artery, vein, cord and heart blood at this time may not be representative of true condition *in vivo*, when these factors are not operating.

Facilitated diffusion implied no maintenance of gradient across membranes,[17]

the lower fetal concentration was, therefore, suggested to be due to placental and fetal metabolism. In 22 per cent of cases fetal blood glucose concentration in the heart blood was higher than the maternal fasting sugar concentration, There may be three reasons for this phenomenon. Firstly, the maternofetal gradient may be negiligible in these cases, along with this if there is a contribution by gluconeogenesis by the fetal liver the heart blood may have a higher concentration tion than the fasting maternal concentration, secondly the blood glucose concentration during operation was frequently higher than the fasting maternal. If this higher maternal blood glucose did equilibrate with fetal blood sugar, there could be a fetal concentration higher than the fasting maternal. Thirdly there could be placental contribution by glycogenolysis. But the placenta was not adding sugar to fetal circulation as shown by the umbilical cord concentration being lower than the maternal sugar concentration during operation (Table I). It is not known, however why fetal liver in some cases adds glucose whereas in other cases do not do so. The two groups of cases may have differed in the content of glucogenic hormones, i.e. the glucocorticoids thyroxine and growth hormone which responded to the stimulus of anesthesia.

These fetuses were delivered by the operation of hysterotomy which necessited the routine administration of intravenous fluid solutions during the operation. The interval between the start of infusion and the delivery of the fetus was between 20-30 minutes during which period the mother was receiving the infusion at the rate of about 2 ml/min. Under normal circumstances, in a person receiving either Ringer's lactate or dextrose saline infusion at about this rate, there is hardly any change in blood glucose concentration. The rate of glucose entry into and egress out of the system remains balanced and blood glucose remains more or less the same. In mothers, however, at labor such an infusion produced some increase of blood sugar concentration and the increase was also reflected in the fetus.[7] The increase, however was not profound and similar in direction in both mother and fetus. In all of our cases the maternal blood glucose concentration during operation was higher than the fasting level, (there was a rise of about 1·5 to 2·1 m moles of glucose/litre) no matter whether Ringer's lactate or 5 per cent glucose saline were infused, unfortunately fasting blood glucose concentration in mother being infused with normal saline was not available.

Administration of anesthesia is a stressful situation. It is therefore, highly probable that anesthesia would exert some effect on blood glucose concentration of the mother. Moreover the anesthetics might traverse the placental circulation and might reach the fetus.[18,19] Thus the problem of glucose homeostasis in the fetus under such circumstances is a very complicated affair, because it is not possible to get a fetus by hysterotomy without administration of anesthesia. Of three anesthetics used, general anesthesia, epidural and open ether, epidural with xylocaine was considered to be the least stressful as it per se is said to have no effect on the fetus.[20] But the blood glucose concentration in our cases above the fasting level was greatest with open ether anesthesia followed by epidural and general anesthesai in decreasing

order. Previous studies had shown the occurrence of fetal hypoxia associated with spinal or epidural anesthesia with concomitant increased umbilical glucose/oxygen quotient.[4] Spontaneous fluctuations in maternal glucose concentration in the guineapig under anesthesia are quickly reflected in the solution perfusion the fetal aspect of the placenta.[21] Hypoxia in mother by breathing air with low oxygen content produced expected rise of blood glucose in the mother, but there was no increase in fetal blood sugar under these circumstances although fetus oxygen tension was almost halved.[5] Our present investigations show that fetal blood glucose concentration in all these instances was lower than the maternal during operation but in about 20 per cent of cases was higher than the fasting maternal. This study also demonstrates the glucose levels of the different compartments in the feto-maternal unit and their interrelationships in specific experimental conditions. Such studies should, therefore, take into account many dependent and independent variables, before conclusion is drawn about fetomaternal relationship of blood sugar concentration.

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DIAGNOSTIC IMAGING IN DEVELOPING COUNTRIES

For those contemplating the purchase of diagnostic imaging systemes, the Scientific Group of W.H.O. established the following order of priorities:

Ideally, the small hospital should have a WHO—Basic Radiologic System (BRS) for routine radiography and, if finances permit, a general-purpose ultrasound unit.

The larger hospital will need more complex X-ray equipment, but will still gain a great deal from an additional general-purpose ultrasound unit.

The major university hospital or other large and well-equipped central hospitals with advanced special-purpose X-ray facilities will need a special-purpose ultrasound unit. At this stage they may also need a general-purpose CT unit, but only where there is very good health care throughout the country should a CT scanner be considered at all.

Finally, in centres where there are highly specialized units of all types and where every specialist medical service is available, the special-purpose CT scanner will come into its own. It is possible that within the next decade magnetic resonance imaging may join the special-purpose CT scanner in these very large institutions, but further simplification of this imaging equipment and a reduction in its running costs will be essential if it is to become widely distributed.

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