# ESTIMATION OF UTERINE BLOOD FLOW IN NORMAL HUMAN PREGNANCY AT TERM<sup>1</sup>

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The blood flow to the pregnant uterus is of evident importance in supplying to the fetus the raw materials required for its growth and development and in removing from the fetal environment the waste products of metabolism. Description of the uterine blood supply was largely in anatomical terms until Barcroft and co-workers measured it directly in the rabbit (1), and indirectly in the sheep (2). It has also been calculated in the sheep (3, 4) from data obtained by fetal plethysmography (5).

#### METHODS

# I. Theory

Estimation of human uterine blood flow at term has awaited the development of methods other than those used in animals. Recently, attempts (6, 7) have been made to apply the Fick principle (8) to the study of the maternal uterine circulation. Figure 1 presents this principle. It is modified from a derivation published by Kety (9) in a discussion of cerebral blood flow. This equation is applicable to any organ if (a) the amount of some blood-borne substance X taken up (or released) in a known time interval by that organ can be determined and if (b) the concentrations of substance X in blood *entering* and blood *leaving* the organ can be determined over the same period of time.

The most familiar application of the Fick equation is in the determination of cardiac output. Here, since the blood flow to all body tissues is being studied, the oxygen consumption of the body may be used as the numerator of the equation and the difference in oxygen content between arterial and "mixed" venous blood is used as the denominator. The ideal test substance for use in the study of an individual organ is a blood-borne metabolite, the rate of production or destruction of which by that organ is measurable and the concentration of which in blood going to that organ and in mixed venous blood leaving that organ can be determined. As an example, hepatic blood flow has been calculated from knowledge of (a) the difference in concentrations of *urea* in blood entering and blood leaving the liver and (b) the rate of formation of urea, a process limited to the liver (10).

Kety (9) has used a foreign substance, nitrous oxide gas, for determination of *cerebral* blood flow by the Fick principle. This substance is normally not present in the body and is not metabolized in body tissues. The method can be applied to the *uterus* if the amount of nitrous oxide in the uterus at the end of the experiment can be determined and if the concentrations of nitrous oxide in arterial blood supplying and venous blood draining the uterus during the experiment can be measured. For such an application the equation derived above (Figure 1) would be modified to the following:

Uterine Blood Flow

$$= \frac{N_2O \text{ in uterus}}{(N_2O) \text{ artery } - (N_2O) \text{ uterine vein}} \quad (Equation 1)$$

The numerator consists of the total nitrous oxide content of the uterus and its contents at the end of the period of nitrous oxide inhalation. The denominator is the integrated arteriovenous nitrous oxide difference during the period of nitrous oxide inhalation.

#### II. Procedure

Observations leading to an estimation of uterine blood flow have been made at elective repeat Caesarian section at term in normal multiparous women. Spinal or epidural anesthesia is used. A mixture of 15 per cent nitrous oxide, 21 per cent oxygen, and 64 per cent nitrogen is administered in an open system through an anesthesia bag and tightly fitting mask equipped with inspiratory and expiratory valves. The mask is held in place by the anesthetist and administration of the nitrous oxide mixture started exactly at experimental time zero and continued for a period of thirty minutes plus the additional time required for delivery of the baby and placenta at the end of the thirty minutes. The total period of nitrous oxide administration is usually less than 40 minutes. No maternal or fetal complications have been observed. Kety has found that administration of 15 per

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Amount of test substance X = Amount of X brought to \_ Amount of X taken away left in organ = Amount of X brought to \_ from organ by venous blood

<u>Now:</u> Amount of X brought to organ by arterial blood = Blood flow x (X)<sub>Arterial</sub> Amount of X taken from organ by venous blood = Blood flow x (X)<sub>Venous</sub>

So: Amount of X left in organ during experiment = Blood flow x  $[(X)_A - (X)_V]$ 

$$\frac{\text{Or:}}{\left[\left(X\right)_{A}^{A}-\left(X\right)_{V}\right]}$$

FIGURE 1

cent nitrous oxide causes no appreciable physiologic or mental effects.

Arterial samples are taken from a brachial artery through an inlying 20-gauge needle attached to a threeway stopcock manifold as described by Kety (9). Under direct vision a polyethylene catheter is threaded into a large parametrial vein (a branch of the uterine venous plexus) through a small tributary adjacent to the uterus. The catheter is inserted to the extent that several inches of it lie within the lumen of a large tributary to the uterine vein. The small tributary is ligated proximal to the point of entry of the catheter, and again around the catheter.

A sample of uterine venous blood is drawn for use as the "venous blank." Then the administration of the nitrous oxide mixture is begun. The instant of beginning administration is called "experimental time zero." From time zero and continuing for one minute the first pair of simultaneous samples is drawn from the uterine vein and brachial artery. Pairs of samples are then drawn simultaneously from artery and vein at a rate of 2 cc. every 15 seconds from the second to third, fifth to sixth, tenth to eleventh, fifteenth to sixteenth, twentieth to twentyfirst, twenty-fifth to twenty-sixth, and thirtieth to thirtyfirst minutes of nitrous oxide administration. Each syringe is carefully labeled as to the source and the serial number of the sample it contains. Each sample is of 8 cc. volume. The blood is drawn anaerobically into oiled heparinized syringes through the three-way stopcock manifolds described by Kety, one of which samples arterial, the other venous blood. Eight pairs of samples taken over the thirty-minute period of study have been found adequate to permit the accurate plotting of the curves of nitrous oxide concentration in artery and vein.

The nitrous oxide inhalation is continued for several minutes after these samples have been obtained. During this extra period an aliquot of amniotic fluid is aspirated through the uterine wall using a blunt No. 14 needle. The uterus is then incised and the baby extracted. Before the infant takes its first breath two pairs of hemostatic clamps are placed on a segment of umbilical cord, and the cord is cut between each pair. Administration of the nitrous oxide mixture is then discontinued. Samples of umbilical arterial and umbilical venous blood are taken anaerobically by puncture of the individual vessels in this excised loop of cord. The placenta is removed and weighed.

Analyses for nitrous oxide are done in duplicate on the sixteen maternal blood samples, the amniotic fluid sample, and the samples of fetal arterial and venous blood from the umbilical cord. Kety's modification of the method of Orcutt and Waters (11) is applied, using 2 cc. samples. Since nitrous oxide is not absorbed in the analysis, its content is calculated by subtracting a blank value of inert gas obtained by analysis of blood taken before beginning the nitrous oxide administration. This blank value has been found to be identical for maternal blood, amniotic fluid and fetal blood in samples obtained at Caesarian sections performed on patients who had not received nitrous oxide. Therefore the "venous blank" is used in calculating the nitrous oxide contents of samples taken from all sources. Oxygen and carbon dioxide contents are measured by the method of Van Slyke and Neill (12) on 1 cc. samples of maternal arterial blood, uterine venous blood and arterial and venous blood from the umbilical cord.

## III. Calculation of the arteriovenous nitrous oxide difference across the uterus

To determine the denominator of (Equation 1) the method used by Kety is directly applicable. The nitrous oxide values for arterial and venous blood are plotted against time, using the midtime of the interval over which each sample was taken as the time of that sample. A typical set of curves is shown in Figure 2. From these the denominator of (Equation 1) is obtained by the trapezoid rule.<sup>5</sup> This gives the arteriovenous difference of nitrous oxide over the period of administration. In the set of curves used in Figure 2 as an example, that value is 36.10 cc. of nitrous oxide per 100 cc. of blood over the thirty-two-minute period of this experiment.

<sup>5</sup> In practice the average arteriovenous nitrous oxide difference for each minute of the experiment is measured from the curves and these values are added to give the nitrous oxide difference for the period of nitrous oxide inhalation beginning at experimental time zero and ending when the umbilical cord is clamped.



FIGURE 2

IV. Estimation of the amount of nitrous oxide in the uterus

The amount of nitrous oxide in the uterus and its contents at the end of the period of study must be determined to supply the numerator of (Equation 1).

In the case of the brain, Kety has avoided this necessity by modifying (Equation 1). He has found that the brain reaches nitrous oxide equilibrium with the blood draining it within a 10-minute period of nitrous oxide administration. When equilibrium is reached the concentration of nitrous oxide in the brain is the same as its concentration in the internal jugular venous blood at the time of equilibrium. With this knowledge, the equilibrium concentration of nitrous oxide in blood is substituted as the numerator of (Equation 1). Since cerebral concentration of nitrous oxide is substituted for total cerebral content of nitrous oxide, cerebral blood flow must be expressed as cubic centimeters of blood flow per 100 gm. of brain. This modification can only be applied if equilibrium is reached during the period of nitrous oxide administration.

We have found that when nitrous oxide is administered to the pregnant woman at term Caesarian section, equilibrium between her blood and the uterine contents does *not* occur for at least one hour. There is a consistent difference between the nitrous oxide concentrations of the umbilical arterial and umbilical venous blood of the infant removed at the end of periods of nitrous oxide administration up to one hour in duration. Furthermore, although, as we have reported, (6) the solubility of nitrous oxide is identical in blood, myometrium and a homogenate of all fetal tissues,<sup>6</sup> even after one hour amniotic fluid does *not* reach nitrous oxide equilibrium with maternal blood. The average concentration of nitrous oxide in the amniotic fluid at the end of our experiments was 1.63 cc. of nitrous oxide per 100 cc. of amniotic fluid, as compared with an average concentration in uterine venous blood of 4.48 cc. of nitrous oxide per 100 cc. of blood. Thus the calculation of uterine blood flow on the assumption that tissue-blood equilibrium is reached in a 30-minute period of nitrous oxide administration is not acceptable. Blood flow so calculated will err in the direction of being falsely high. An alternative method has been developed as follows:

#### a. Experimental data available for calculation:

In our experiments the uterus is opened and its contents "sampled" at the end of the experiment. The infant and placenta are individually weighed and the concentrations of nitrous oxide are measured in the umbilical arterial and venous blood samples and the amniotic fluid sample.

#### b. Assumptions currently necessary:

1. That fetal and placental tissues are in nitrous oxide equilibrium with umbilical arterial blood after thirty minutes of nitrous oxide administration to the mother. determined by exposing these tissues to a known tension of nitrous oxide in a tonometer at 37 degrees centigrade and then analyzing the equilibrated tissues for their nitrous oxide content according to the method presented by Kety, Harmel, Broomell, and Rhode (13). The partition coefficient for nitrous oxide (the solubility of nitrous oxide in the tissue divided by the solubility of nitrous oxide in blood) was found to be 1.0 for the uterus, 0.99 for amniotic fluid and 0.96 for the whole fetus.

<sup>&</sup>lt;sup>6</sup> The solubility of nitrous oxide in amniotic fluid and in homogenates of whole fetus and myometrium was

	N <sub>2</sub> O in uterus	/Founding ()
Uterine Blood Flow =(N2C	- (Equation 17	
		Example - J.B. 12/13/52
N2O in amniotic fluid plus	<b>_</b> Vol. amniotic fluid x N₂O in amniotic fluid	750 cc. x = 14 1.9 cc/100 cc
N <sub>2</sub> O in fetus and placenta plus	∎ Wt. fetus + placenta x N₂O in umbilical artery	3620, gms. x = 122 3.4 cc/100 cc
N <sub>2</sub> O in myometrium	"Wt. myometrium x N <sub>2</sub> O in maternal artery	1000 gms. x = 56 5.6 cc/100 cc
N <sub>2</sub> O in uterus at end of experiment		192cc

#### FIGURE 3

This blood has circulated through the fetal body and is now returning to the placenta. This assumption is supported by experiments in animals, in which the fetal nitrous oxide content is directly determined and compared with the nitrous oxide concentration of umbilical arterial blood; <sup>7</sup>

2. That the myometrium is in nitrous oxide equilibrium with maternal arterial blood at the end of 30 minutes. This equilibrium time has been found to be adequate for myocardium and brain. We have found that the solubility of nitrous oxide in an homogenate of myometrium is identical with its solubility in blood. The maternal arterial concentration of nitrous oxide is therefore accepted as expressing the concentration of nitrous oxide in the myometrium;

3. That the average uterus weighs 1.0 Kg. at term pregnancy. This figure was taken from Reynolds (14);

4. That the average volume of amniotic fluid at term is 750 cc. The volume of amniotic fluid varies within wide limits. However, in this study the error so created is relatively small because of the low nitrous oxide content of amniotic fluid. Examination of the experiment cited below as an example will show that variation in assumed amniotic fluid volume from 100 cc. to 1,500 cc. will make an ultimate difference in calculated uterine blood flow of only 70 cc. per minute;

5. That the specific gravity of the fetus, placenta, and myometrium is equal to the specific gravity of the maternal blood. The error of this assumption is negligible.

With the facts at our disposal and the assumptions listed above, the calculations shown in Figure 3 can be made, keeping in mind that the total nitrous oxide content of the pregnant uterus is equal to the sum of the nitrous oxide contained in the fetus, the placenta, the uterus itself, and the amniotic fluid.

Having now calculated the nitrous oxide content of the uterus at the end of the period of study we can use this as the numerator in (Equation 1). In the case used as an example:

Uterine Blood Flow

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$$= \frac{N_2O \text{ in uterus}}{(N_2O) \text{ artery} - (N_2O) \text{ uterine vein}} \times 100 = 530 \text{ cc. per minute.}$$

## V. Additional data derived from estimated uterine blood flow

Analyses for oxygen and carbon dioxide content are done on the arterial and uterine venous blood samples and on the umbilical arterial and umbilical venous blood. With this knowledge the following calculations can be made:

1. Uterine oxygen consumption = Uterine blood flow  $\times [(O_2) \text{ artery } - (O_2) \text{ uterine vein}];$ 

2. Uterine carbon dioxide production = Uterine blood flow  $\times$  [(CO<sub>2</sub>) uterine vein - (CO<sub>2</sub>) artery];

3. Uterine 
$$RQ = \frac{\text{Uterine carbon dioxide production}}{\text{Uterine oxygen consumption}};$$

Fetal RQ  
= 
$$\frac{(CO_2) \text{ umbilical artery } - (CO_2) \text{ umbilical vein}}{(O_2) \text{ umbilical vein } - (O_2) \text{ umbilical artery}}$$

5. An approximation of the volume of *fetal* blood flowing to the placenta can be reached by assuming that all oxygen used by the uterus is consumed by the fetal tissues. Actually, some oxygen will be consumed by the myometrium so this assumption gives a figure which will err in being too large. It is called "Maximum umbilical blood flow."

"Maximum umbilical blood flow"

 $= \frac{\text{Uterine oxygen consumption}}{(O_2) \text{ umbilical vein } - (O_2) \text{ umbilical artery}} \times 100.$ 

 $<sup>^{7}</sup>$  In experiments performed on two goats and four sheep the nitrous oxide concentration of umbilical arterial blood was compared with the nitrous oxide concentration of the whole fetus. In four of the six experiments the figures agreed within 0.5 vol. per cent.

Experiment number	Birth weight of infant Kg.	Uterine blood flow cc./minute	Uterine O2 consumption cc./minute	Uterine CO <sub>2</sub> production cc./minute	Uterine respiratory quotient	Uterine O2 consumption Birth weight of infant cc./minute/ kilogram	UBF <b>E</b> † cc./100 gm./ min.
7	3.5	590	17.7	8.3	0.5	5.1	13.4
8	3.1	535	18.2	20.0	1.1	5.9	15.5
10*	3.0	330	16.4	10.8	0.7	5.5	8.8
11*	3.2	560	21.3	23.0	1.1	6.5	13.9
12*	3.1	480	16.4	12.5	0.76	5.3	12.7
14*	3.6	510	31.0	38.0	1.2	8.5	10.9
16	3.7	315	14.8	13.9	0.94	4.0	9.0
18	3.7	840	22.7	27.7	1.2	6.1	22.0
19	2.9	255	13.0	8.7	0.67	4.5	7.8
21	3.2	770	57.0	47.0	0.83	18.0	19.5
24	3.5	700	44.0	40.6	0.92	12.5	13.0
25	2.9	335	21.8	21.5	0.98	7.5	8.0
26	3.3	175		10.9			6.4
20	3.51						
	& Twins	1,150	48.3	47.2	0.98	6.9	18.0
Mean of single	,						
pregnancies	3.3	492	24.5	21.8	0.91	7.5	12.4
deviation	.28	195.4	12.7	12.5	0.19	3.8	4.45
Standard error	.078	54.2	3.67	3.47	0.055	1.1	1.23

 TABLE I

 Uterine blood flow and related figures

\* Nitrous oxide concentration of umbilical arterial blood assumed to be 3.5 cc. per 100 cc.

† Uterine blood flow calculated upon the assumption of nitrous oxide equilibrium between maternal blood and uterine contents.

### RESULTS

The procedure described has been attempted at elective repeat Caesarian section at term in twentyfive women. In ten of these, results are sufficiently complete to permit calculation of uterine blood flow and the supplementary data derived from a knowledge of uterine blood flow. These are summarized in Table I. Four additional experiments (Nos. 10-14) lacked only a determination of umbilical arterial nitrous oxide concentration. These four cases were included by using the average nitrous oxide concentration (3.5 cc. per 100 cc.) found in other experiments in which the same period of nitrous oxide inhalation was employed prior to delivery of the fetus. The variation in this nitrous oxide concentration was small (2.8 to 3.9 cc. N<sub>2</sub>O per 100 cc. blood in nine experiments).

One of the subjects studied in whom data for calculation of uterine blood flow is complete had a twin pregnancy. The uterine blood flow and values calculated from it are listed separately in this case.

Uterine blood flow determined upon the assumption of nitrous oxide equilibrium between maternal blood and uterine contents is included in the column marked  $UBF_E$  for comparison with figures in the literature (7).

## DISCUSSION

From a consideration of Table I, it can be seen that the uterine blood flow calculated by this method and using these assumptions varies widely from patient to patient. Such variation is to be expected in any physiological function studied in a series of individuals. All patients studied were normal multiparae undergoing repeat Caesarian section at term. Spinal anesthesia was used in the cases reported here. The variability in results may be due, in part, to limitations in the experimental technique, particularly in sampling "mixed" venous blood from the pregnant uterus. That samples drawn from any single vein are representative of the average (or "mixed") venous blood is open to question.

On one occasion samples were drawn simultaneously from each of two large veins which drained the right and left uterine parametrial regions respectively. The concentrations of nitrous oxide were identical in the two veins. We have tried to minimize this possible error by selecting only large veins and by passing the catheter well downstream in them, so that an average of several large tributary blood streams could be expected.

Even with this possible source of error only two of the calculated flows are below 300 cc. per minute, and only three of the single pregnancies studied have a calculated flow above 600 cc. per minute. The average for all single pregnancies studied is approximately 500 cc. per minute. This average figure is probably an accurate one within the conditions of the study.

Assali, Douglass, Baird, Nicholson, and Suyemoto (7) has also attempted to measure uterine blood flow using nitrous oxide. They made the assumption that nitrous oxide equilibrium exists between uterus and blood at the end of thirty minutes of nitrous oxide administration, and have reported an average flow of 15 cc. per 100 gm. per minute in a series of seven women studied during the last month of pregnancy. If the average weight of the pregnant uterus is 5 kg., a blood flow of 500 cc. per minute would give a figure of only 10 cc. per 100 gm. per minute. As discussed above the assumption of nitrous oxide equilibrium would be expected to give erroneously high results.

The average oxygen consumption per minute of the pregnant uterus in our subjects is 24.5 cc. per minute, and carbon dioxide production, similarly calculated, averages 21.8 cc. per minute. Thus the average respiratory quotient in the uterus at term is 0.91.

Comparison of the oxygen consumption per minute as calculated here with previously reported figures is difficult. Assali and his associates calculated an oxygen consumption of 1.9 cc. per 100 gm. per minute which is far in excess of values recorded in the present study. If we assume, as they do, that the weight of the pregnant uterus is 5 kilograms, its oxygen consumption would amount to 95 cc. per minute on the basis of their average figure for oxygen consumption. Cugell, Frank, Gaensler, and Badger (15) have reported an average increase in maternal oxygen consumption at term of 65 cc. per minute in nonbasal subjects. Such subjects are comparable to those used in Assali's study. In basal subjects the increase in maternal oxygen consumption at term averaged 38 cc. per minute in the patients reported by Burwell, Strayhorn, Flickinger, Corlette, Bowerman, and Kennedy (16).

The marked difference between the figure for oxygen consumption presented here and that obtained by Assali is due not only to the larger uterine blood flow he reported but also to the large arteriovenous oxygen difference (average 12.7 vol. per cent) across the uterus in his seven cases. The average arteriovenous oxygen difference in our series is 4.8 vol. per cent in the single pregnancies. Barron (4) found an average arteriovenous oxygen difference of 3.8 vol. per cent across the uterus of five sheep near term.

Determinations of the oxygen consumption of the fetus were made by Barcroft, Herkel, Hill, Kennedy, and Mason (1, 2, 17) by a variety of methods. Values ranged from 4 to 8 cc. per kg. per minute in the sheep at term to about 8 cc. per kg. per minute for the rabbit embryo at term. Calculation of oxygen consumption in the human newborn gives figures of between 6 and 8 cc. per Kg. per minute (18), a figure of the same magnitude as that determined for the sheep and rabbit. If we assume that the myometrium weighs 1 kg., that the average placental weight is 550 grams, and that these tissues consume oxygen in the same proportion to weight as does the fetus, the average oxygen consumption per kilogram of tissue is 5.05 cc. per Kg. per minute. This figure appears to be of the proper order of magnitude, when compared with the animal observations mentioned above.

The uterine respiratory quotient is included in the Table for the sake of completeness. At present all that can be said about it is that the average respiratory quotient is similar to that of the whole adult under conditions of the "steady state."

The uterine blood flow calculated for the patient with a twin pregnancy is worthy of comment. Each of the babies weighed 3.5 Kg. at birth, and each had a concentration of nitrous oxide in its umbilical arterial blood at delivery which was comparable to that seen in the single pregnancies studied. Thus it appears that the quantity of maternal blood circulating through the uterus per minute is about twice that of the average single pregnancy. This finding is strengthened by the fact that the arteriovenous oxygen difference across the uterus in this patient is almost identical with the average found in the single pregnancies.

## SUMMARY

A method for estimating the quantity of maternal blood flowing through the pregnant uterus at term has been developed. Estimation of uterine blood flow permits the calculation of several important features of gestational metabolism.

Results obtained by applying this method to 14 normal women at term Caesarian section are reported. The average uterine blood flow in 13 single pregnancies was estimated at 500 cc. per minute and the average oxygen consumption of the uterus and its contents was calculated to be 25 cc. per minute. In one patient with a twin pregnancy the uterine blood flow and uterine oxygen consumption were approximately twice the magnitude of the average of the single pregnancies.

The calculated uterine oxygen consumption per kg. of tissue is in general conformity with data previously obtained by other methods in lower animals.

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