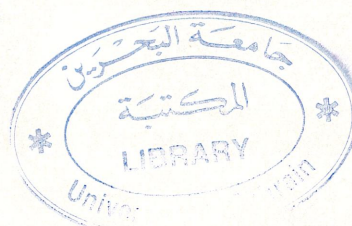


BIOCHEMICAL CHANGES DURING LABOUR IN PREGNANT WOMEN UNDER NORMAL AND ABNORMAL METABOLIC CONDITIONS

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B Sc. Pharmacy

A THESIS
SUBMITTED TO THE DEPARTMENT OF TOXICOLOGY
AND BIOPHARMACEUTICS AND THE COMMITTEE
OF GRADUATE STUDIES OF THE COLLEGE
PHARMACY IN PARTIAL SATISFACTION
OF THE REQUIREMENTS FOR THE
DEGREE OF MASTER OF
SCIENCE IN PHARMACY

JUNE 1980



I certify that this thesis was prepared under my supervision at the University of Baghdad as a partial requirement for the degree of Master of Science in Pharmacy " Toxicology " .

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We, the Examining Committee, after reading this thesis and examining the student in its content, find it adequate with standing as a thesis for the degree of Master of Science in Pharmacy " Toxicology ".

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ABBREVIATIONS

The following abbreviations are used throughout the text of this thesis:

ADP	Adenosine diphosphate
ATP	Adenosine triphosphate
ACTH	Adrenocorticotrophic hormone
FFA	Free fatty acids
GK	Glycerokinase
ht	Height
hr	Hour
HBDH	Hydroxybutyrate dehydrogenase
HGH	Human growth hormone
HPL	Human placenta lactogen
i.v.	Intravenous
LDH	Lactate dehydrogenase
NAD	Nicotinamide adenine dinucleotide
NADH	Nicotinamide adenine dinucleotide (reduced)
min	Minute
PCA	Perchloric acid
PEP	Phosphoenol pyruvate
PK	Pyruvate kinase
rpm	Revolution per minute
SEM	Standard error of the mean
wt	Weight
Yr	Year
L	Litre
ml	Millilitre -10^{-3} L.
Kg	Kilograms
g	Gram

mg	Milligram	$-10^{-3}g$
m	Meter	
cm	Centimeter	$-10^{-3}m$
nm	Nanometer	$-10^{-9}m$
M	Mole or Molar	
umol	Micromol	$-10^{-6}mol$
n mol	Nanomol	$-10^{-9}mol$

CHAPTER 1

I N T R O D U C T I O N

METABOLISM OF GLUCOSE - GENERAL CONSIDERATION

Glucose is the principal energy source for the cell by its breakdown into smaller metabolites and ultimately to CO_2 , water and energy in the form of ATP, is made available for metabolic processes.

An important limiting factor in glucose metabolism is the rate of its entry into the cell, several hormones such as insulin and metabolic substances like FFA, Ketone and Lactate are known to influence this process (Randle, Newsholme and Garland 1964; Randle, Garland, Hales, Newsholme Denton and Pogson, 1966). After glucose has penetrated into the cell, phosphorylation with the formation of glucose - 6 - phosphate (G-6-P) is considered as essential preliminary for the entry of glucose into the majority of subsequent metabolic events G-6-P can then take part in at least five different metabolic pathways though the distribution and the relative importance of these routes varies in different tissues and may also alter in responses to different physiological and nutritional states.

The major route for glucose degradation in the body is the glucolytic pathway, i.e., the series of metabolic events which start with G-6-p and end up with the production of pyruvic acid. These reactions are identical in the presence or absence of oxygen, thereafter, the products vary with the available oxygen supply and pyruvic acid,

either reversibly converted to lactic acid or decarboxylated to form acetyl CoA. The former reaction predominates in anaerobic condition where as the latter reaction predominates in aerobic condition. Thus in anaerobic conditions energy requirements may be met by increased breakdown of tissue glycogen and glycolysis proceeds more rapidly than in aerobic conditions. A typical example of this is seen in rapidly contracting skeletal muscle, similar considerations apply to uterine muscle, especially in labour as a form of sustained vigorous exercise.

BLOOD GLUCOSE REGULATION

The level of circulating glucose is kept remarkably constant despite varying rates of tissue glucose metabolism and the irregular supply of carbohydrate absorbed from the gastro intestinal tract. The regulation of blood glucose is achieved by a complex interplay between intrinsic changes in hepatic carbohydrate metabolism and the effects of hormones e.g. growth hormone, glucagon catechol amines and glucocorticoid. Thus a fine balance between glycogenesis and glycolysis on the one side and glycogenolysis and gluconeogenesis on the other side is maintained.

FAT METABOLISM - GENERAL CONSIDERATION

The lipid reserves of the mammalian body are usually stored as neutral fat of triglyceride in adipose tissue.

For many years, the tissue lipids were considered to be inactive storehouse of calorogenic material, called upon in times of shortage of metabolic fuels.

On the contrary, the triglycerides of adipose tissues act as a labile store of oxidizable substrates which can be rapidly mobilized and re-synthesized, although the total amount of fat in the body remains roughly constant from day to day when caloric balance is maintained.

The triglyceride undergoes hydrolysis by a hormone sensitive lipase to form free fatty acids (FFA) and glycerol. Since glycerol can not be utilized readily in the tissue, it diffuses out into the blood stream, because the enzyme glycerokinase only present in the liver. Thus increased blood glycerol concentration can be used as an index for increased fat mobilization (Vaughan, 1962).

Under conditions of adequate nutritional intake or when the utilization of glucose by adipose tissue is increased, the FFA outflow decreases and the level of plasma FFA falls. However the release of glycerol continues, demonstrating that the effect is due to the availability of α -glycerophosphate from glucose which facilitate re-esterification of FFA (Robinson and Newsholme, 1967).

From all the facts, it would appear that when carbohydrate is adequate, adipose tissues tend to facilitate the utilization of glucose for energy production and

to esterify FFA. However when carbohydrate is in short supply, it spare glucose for esterification and utilizes fatty acids for energy production.

The rate of release of FFA from adipose tissue is affected by many hormones, that influence either the rate of esterification or the rate of lipolysis. Hormones with adipokinetic action include adrenaline, noradrenaline, growth hormone , glucagon, glucocorticoid and human placenta lactogen (HPL). Some of these hormones act directly by activating the enzyme lipolytic lipase, others may act indirectly by antagonizing the effect of insulin on adipose tissue (Corbin, Reimann, Walsh and Krebs, 1970).

The release of FFA from adipose tissue is inhibited by insulin and this due mainly to its stimulating effect on the inflow of glucose into the adipose tissues, but insulin may also have some direct inhibitory effect on intracellular lipase (Butcher, Snyder, Park and Sutherland, 1966).

The biochemical mechanisms involved in the mobilization of fatty acids from adipose tissue and the various hormonal changes involved have been studied extensively in human when they are at the steady state.

The metabolic importance of the mobilized fatty acids and their metabolites however have not deeply explored in responses to physiological stresses. In conditions

such as starvation or prolonged muscular activity, the plasma FFA is usually increased. The raised fatty acids provides not only an immediate source of available metabolic fuels but also to provide the necessary signal for the tissue to adapt and oxidise the fatty acids and later the smaller metabolites such as ketone bodies (Gorden, Cherkas and Gate, 1957).

METABOLISM IN PREGNANCY

Considerable changes occur in maternal carbohydrate and fat metabolism during pregnancy as judged by the increased blood levels of lactate, pyruvate and plasma lipids (De Alvarez, Goodell and Zighelboim, 1967). The rise being particularly marked in respect of FFA (Burt and Dannenberg, 1965). Though little is known about the alteration in tissue metabolic events. Fasting blood glucose is not however increased in pregnant women (Bleicher, O'Sullivan and Freinkel 1964). It has generally been accepted that glucose tolerance is impaired in pregnancy (Spellacy 1975) and that pregnancy itself considered a diabetogenic factor for this effect. The fact that diabetic women frequently require increased amount of insulin as pregnancy advances, the occurrence of glycosuria in pregnancy (Zarowitz and Newhouse, 1973) and the increased resistance to insulin in late pregnancy are all cited as evidence in support of this view (Burt and Kimel 1956). However fasting blood glucose is not increased in normal pregnancy (O'Sullivan and Mahan 1964) and studies of carbohydrate metabolism in standard

normal conditions have failed to show reduction in carbohydrate utilization in healthy women during gestation (Quinto, Bottiglioni and Orlandi 1967 a,b).

It has been suggested that the loss of sensitivity to insulin in pregnancy is due to an increased blood level of growth hormone (Roth, Glick, Yalow and Berson 1963).

This would certainly explain the raised plasma FFA concentration in pregnancy, since growth hormone enhances FFA release from fat stores by inhibiting the entry of glucose into adipose tissue cells, but the blood level of growth hormone is hardly raised in pregnancy (Kaplan and Grumbach, 1965; Yen Samaan and Pearson, 1967). It remains possible, however that other diabetogenic hormones including ACTH and glucocorticoid (Doe, Dickinson, Zinneman and Seal, 1969) are responsible for fat mobilization.

HPL and glucagon also contribute to the loss of sensitivity to insulin which is probably secondary to increased mobilization of FFA.

In view of functional immaturity of many foetal organs particularly of the liver and the consequent incomplete development of many metabolic pathway, the foetus is certainly unable to carry out all essential synthetic function and depends on the mother for its energy demands. It is already known that the foetus derives its energy almost exclusively from carbohydrate metabolism and thus requires a continuous supply of glucose for this purpose.

Furthermore, that the foetal tissue particularly the brain may in fact utilize glucose in preference to fatty acids and ketones (James, Raye, Gresham, Makowski, Meschia and Battaglia, 1972).

It is not surprising, in view of the role of glucose and fatty acids in vital metabolic processes that abnormalities of fat and carbohydrate should have been found in women with altered nutritional conditions, such as obesity.

Raised fasting level of plasma FFA (Issekutz, Miller and Paul, 1966 ; Seyffert, Madison, 1967) impaired tolerance to glucose challenge associated with hyperinsulism (Nestel, Carroll and Silverstein, 1964) and resistance to ketone bodies has been demonstrated in human obesity (Krebs 1964).

The pattern of the whole body metabolism during labour has been little studied. Labour presumably stimulate an endocrine and metabolic responses essentially similar to that noticed during stressful physical activity.

Exercise, namely increased adrenal activity and increased anterior pituitary hormones, with a resultant increase in both glycogenolysis and gluconeogenesis. The extent to which the metabolic demands imposed by obesity could modify this pattern is not however clear.

Objective

Physical stress of various kinds had been associated with a wide variety of metabolic and hormonal responses (Johnson, Walton, Krebs and Williamson, 1969 ; Rennie, Sulaiman, Johnson and Park, 1974). In acute forms of physical stress and due to the need for extra energy, the whole metabolic processes and the mechanism regulating the fuel supply are accelerated (Rennie, Jennett and Johnson, 1974).

The two major circulating fuels in the body are glucose and FFA. Alterations in these two variables have been reported in a variety of physiological and altered pathological and nutritional states particularly in response to moderate physical exercise (Sulaiman 1974).

Human labour was chosen, because it offers an excellent opportunity for the understanding of the adaptation of the body to moderate and somewhat severe form of acute stress.

Increased concentrations of blood glucose, plasma FFA and lactic acid during pregnancy and labour have been reported previously (Fairweather 1965 ; Wheley Zuspan and Nelson 1965 ; Kashyap, Sivasambo, Sethy, Cheah and Gortside 1976).

However, these studies have not particularly looked into the dynamic metabolic changes that occur during the

course of labour. There is almost no information on ketone bodies changes during human labour. Thus interpretation of the past observations has been limited regarding the significance of ketone bodies changes during labour, since the utilization of ketone bodies by working muscle and brain tissues have been demonstrated in man (Hagenfeldt and Wahren, 1968 ; Owen and Reichard, 1971).

This work, was performed to establish the dynamic alterations in circulating glucose, pyruvate, lactate, FFA, glycerol, ketone-bodies and cortisol before and during the course of spontaneous human labour and the results were compared with alterations when labour was induced with oxytocin, comparative studies between patients with obesity and normal non-obese subjects during spontaneous labour were also carried out.

CHAPTER 2

SUBJECTS AND TECHNIQUES

SUBJECTS

Forty six (46) pregnant female volunteers of different gestational age were studied in four groups. The nature of the investigation and the particulars of each group are listed in details in chapters.

The subjects were in-patients and were selected by the obstetrician in charge at the University Department of the Medical City, Baghdad. They were all informed about the nature of the investigation and their consent were obtained. All patients who have no obstetric or medical complications were allowed fluid diet during labour.

TECHNIQUES

A - Preparation of blood samples

(10 ml) blood was taken from a forearm vein by a veinpuncture. 5 ml of this blood was immediately added to 5 ml 10% ($\frac{V}{V}$) ice cold perchloric acid in pre-weighed universal container. This was shaken vigorously and sotred in the cold until the protein precipitate could be centrifuged down.

The remaining 5 ml of blood was placed in sodium heparinized tube and centrifuged for 10 min. at 2500 rpm. The seperated plasma was pipetted off and stored at -15°C .

B - Treatment of protein free filtrate

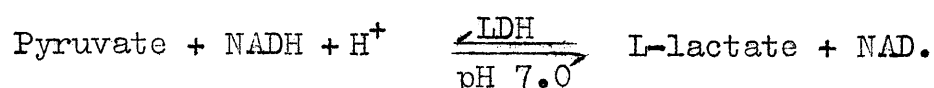
After the removal of denatured blood by centrifugation at 18,000 rpm, for 20 min. The clear supernatant was decanted into a graduated tube and the volume noted. The specimens were neutralised with 20% potassium hydroxide using universal indicator. The tubes were recentrifuged for 5 min and the volume noted again. The insoluble potassium perchlorate was allowed to precipitate completely by allowing the tubes to stand at 4°C for 30 min. The supernatant was then decanted into plastic tubes, which were stored at -15°C for subsequent analysis.

A dilution factor was calculated from the volume of blood taken and the volume of alkali added as follows:

$$\frac{\text{blood volume} + 5}{\text{Blood volume}} \times \frac{\text{Neutral volume}}{\text{Acid volume}}$$

C - Analysis of blood pyruvate and blood acetoacetate

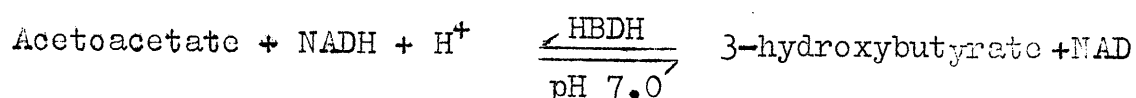
These two metabolites were measured on the same sample by modification of the methods of Hohorst et al., (1959) for pyruvate and Williamson et al., (1962) for acetoacetate. The pyruvate was reduced to lactate with excess of NADH using phosphate buffer (0.1 M pH 7.0).



The reaction was catalysed by excess of the enzyme lactic acid dehydrogenase, and the decrease in optical

density due to the oxidation of NADH measured at 340 nm.

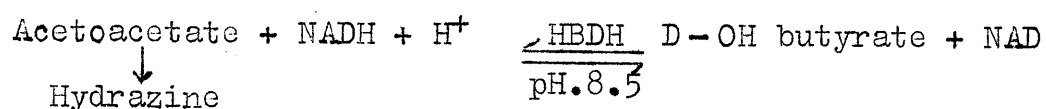
The acetoacetate was analysed under the same conditions by the enzyme D-(-) B-hydroxybutyric acid dehydrogenase, which catalysis the reaction of acetoacete to 3-hydroxybutyrate.



Acetoacetate is slowly decarboxylated to acetone in neutral solution, so this analysis had to be carried out immediately after the acid samples were neutralised.

D - Analysis of blood 3-hydroxybutyrate

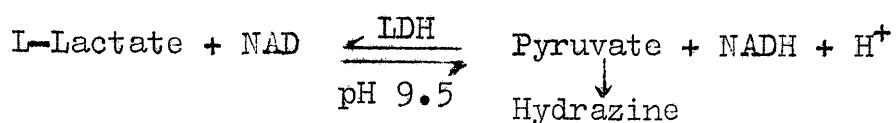
This was determined by the method of Williamson et al., (1962) using the enzyme D-B hydroxybutyric acid dehydrogenase to catalyse the oxidation of 3-hydroxybutyrate to acetoacetate in the presence of excess NAD.



Acetoacetate at zero time was blocked in the form of its hydrozone in alkaline medium by using hydrazine buffer (pH 8.5). The change in optical density due to the formation of NADH was measured at 340 nm.

E - Analysis of blood lactate

This was determined by the method of Hohorst et al., (1959) using the enzyme lactic acid dehydrogenase to catalyse the oxidation of lactate to pyruvate in the presence of excess NADH.



An alkaline medium was used (pH 9.5) and the pyruvate was blocked in the form of its hydrozone using hydrazine buffer at zero time.

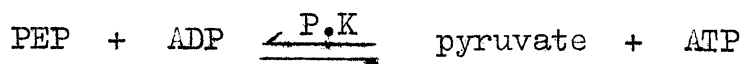
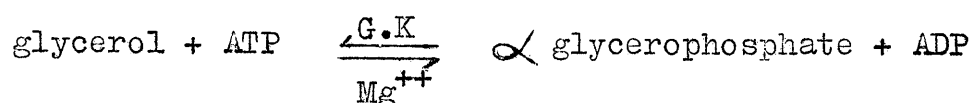
The changes in optical density due to the formation of NADH was measured at 340 nm.

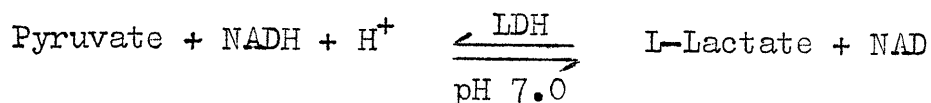
F - Analysis of blood glycerol

This was determined by the method of Kreutz (1962) using the enzyme glycerokinase to catalyse the phosphorylation of glycerol by ATP to L-glycerol-1-phosphate.

The ADP formed was phosphorylated back to ATP with PEP. forming pyruvate which was then reduced to lactate with NADH in the presence of lactic acid dehydrogenase.

The whole reactions were as follows:





Since 1 mole of glycerol $\equiv$ 1 mole of NADH, the optical density change at 340 nm due to the disappearance of NADH was proportional to the glycerol concentration.

G - Analysis of plasma free fatty acids

Plasma FFA were determined by the micro-method of Duncombe (1962).

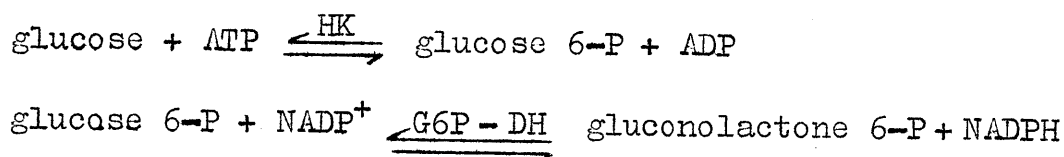
Chloroform was used to extract the plasma FFA. The extracted FFA were complexed with copper triethanolamine to soluble copper salt after separation of the phases by centrifugation and removed of the top aqueous layer by simple water suction, colorimetric estimation was carried out with the dye sodium diethyl dithiocarbamate.

The color developed was immediately measured at 440nm. All FFA determinations were carried out in duplicate using 0.5 ml plasma against palmitate standard of different concentrations.

H - Analysis of blood Glucose

Blood glucose was determined by the method of Schmidt (1961) using hexokinase (HK)/glucose-6-phosphate dehydrogenase (G-6 P -DH) enzymes, and triethanolamine buffer with magnesium sulphate, NADP and ATP. (Kit, supplied by Boehringer, W. Germany).

The first reaction was catalysed by hexokinase enzyme. The next reaction was catalysed by glucose 6 phosphate dehydrogenase.



The formation of NADPH which is equivalent to the amount of glucose catalyzed was measured at 340 nm.

I - Analysis of plasma cortisol

This was determined by radioimmunoassay (Cortipac method). The method is dependent on the competitive binding to transcortin. The plasma was diluted and heated to denature the endogenous cortisol binding protein, then was introduced into vial containing selenium - 75 labelled cortisol bound to transcortin and adsorbent granules. Cortisol from plasma sample and selenium - 75 labelled cortisol compete for the binding sites of transcortin. The free fraction was simultaneously distributed between granules.

At equilibrium, the granules were allowed to settle down and the supernatant was taken for counting in gamma counter using a series of cortisol standards.

The kit was supplied by radiochemical center, Amersham, England.

CHEMICALS

All the chemicals were of the highest available purity

Sodium heparine injection 5000 units/ml "Ubjohn U.S.A."

Perchloric acid 20% "Fluka Switzerland".

Potassium hydroxide "Riedle De Haen W. Germany".

Hydrazine hydrate "Carlo Erba Italy".

Chloroform , Universal indicator , tris Hydroxymethyl (methylamine) , Potassium di-hydrogen phosphate , di-Potassium hydrogen phosphate "BDH - England".

Glacial acetic acid , Sodium diethyl dithio carbamate (trihydrate) , Hydrochloric acid "Merk W. Germany".

Triethanol amine, Cuppric nitrate , Magnesium chloride , Secondary butyl alcohol "Hopkins and Williams, England".

Cortipac Kit for cortisol CPB assay code SC₆ include:

Buffered transcortin - Cortisol ⁷⁵Se and standards.

"Radio chemical center , Amersham , England".

Enzymes and Co-factors

Lactic acid dehydrogenase	10 mg/2ml
3-hydroxy butyric acid dehydrogenase	5 mg/ml
Pyruvate kinase	2 mg/ml
glycero kinase	1 mg/ml
Nicotinamide adenine dinucleotide, reduced	(NADH).
Nicotinamide adenine dinucleotide, oxidised	(NAD).
Adenosine 5 triphosphate disodium salt	(ATP).
Phosphoenol pyruvate , monosalt	(PEP).

Test combination glucose Kit, include "triethanal buffer, MgSO_4 , NADP , ATP , hexokinase glucose 6 phosphate dehydrogenase enzyme.

All the enzymes and Co-factors were supplied by "Boehringer Mannheim , W. Germany".

EQUIPMENT

Centrifuge K₂₄ cooled super with roter number 905/W.R. 24 x 10 ml "Janetzki, E. Germany".

pH. meter with glass electrode No. 401 NW EOZ, model 292 MK₂ "Pye Unicam, England".

Spectro-photometer SP₆ -500 UV. visible, "Pye Unicam, England".

Vortex mixer "Wilten and Co., Holand".

Waterbath with control and water circulation "Kottermann, W. Germany".

Gamma Counter "Searle , England".

CHAPTER 3

METABOLIC AND HORMONAL
RESPONSES IN LATE PREGNANCY

INTRODUCTION

In the introduction to this thesis I have explained, that, the purpose of these investigation was first to establish in human, the normal response of blood metabolites and hormones to labour and second to compare them with responses in altered nutritional state such as obesity. Labour was chosen because it produces greater demands on the metabolic processes.

In this situation any metabolic or hormonal effect of nutritional or pathological states could be expected to be magnified.

Alterations in the major metabolic fuels during the process of labour in human are not fully explored. Furthermore, there is no data available on normal base line values of some fat and carbohydrate metabolites particularly those of ketone bodies during different gestational period and during different stage of labour. This investigation was designed to establish a base line control values for the following blood metabolites, FFA, glycerol, ketone bodies, lactate, pyruvate, glucose and cortisol in women during different gestational period. These values were studied in comparison with available reference values of adult non-pregnant healthy subjects, such observation were necessary to give a background information to studies reported latter in this thesis upon the effect of labour as a stress on body metabolism.

METHOD:

Twelve (12) healthy female subjects with normal pregnancies, were studied at the third trimester of pregnancy Table 3.1 . The results of blood metabolites were compared with available reference values of non-pregnant healthy adults. The subjects were volunteers and non of them suffered from metabolic or hormonal disorders.

Blood samples were taken from a forearm vein after an overnight fast and were treated as previously described in page 19-20 and used for the analysis of FFA, glycerol, glucose, ketone bodies, lactate, pyruvate and cortisol.

RESULTS:

The values listed in table 3.2 represent the overnight fasting concentrations of metabolites measured in venous blood of (12) pregnant volunteers (A). Reference values (in mean) of non-pregnant subjects were used for comparison (B). The results shows clearly that the values of metabolites in pregnant subjects were similar and closely comparable to that of the reference values except that of plasma FFA and blood glucose.

The mean plasma FFA were significantly higher in the pregnant subjects than those of reference value after overnight fast. The results also shows that there was no significant difference between the two groups regarding blood glucose, but the levels were slightly lower than the mean values for non-pregnant women.

Table 3.1
Details of twelve pregnant control subjects

No.	Subject	Age Yr	Weight Kg	Height cm	Gestation week	Reciprocal Ponderal index	over - weight %
1	F.I	36	72	164	27	39.42	109
2	H.H	21	68	162	28	39.69	107
3	N.H	22	66	160	28	39.59	110
4	A.I	33	61	160	32	40.65	101
5	B.N	30	65	160	37	39.79	110
6	I.M	24	72	162	31	38.41	115
7	S.A	25	65	158	38	39.2	112
8	M.J	25	72	160	33	38.7	121
9	F.S	22	63	160	26	40.21	107
10	W.G	28	75	158	31	37.4	136
11	W.K	20	65	160	30	38.03	106
12	S.M	30	70	162	38	39.3	114
	Mean	26.3	68	161.9	31.58	39.21	112.3
	SEM	1.496	1.39	0.519	1.232	0.267	2.6

$$* \text{ Reciprocal ponderal index} = \frac{ht}{\sqrt[3]{wt}}$$

$$** \text{ overweight \%} = \frac{\text{calculated wt}}{\text{ideal weight}} \times 100$$

* Mc Guinness and Sloan, 1971.

** Varley, Gowenlock and Bell 1976.

Table 3.2
(A)

No.	Subjects	FFA umol/L	Glycerol umol/L	Ketone bodies umol/L	Lactate umol/L	Pyruvate umol/L	Glucose mg/100ml	Cortisol n mol/L
1	F.I	709	91.2	74.03	940	84.2	70.5	-
2	H.H	596	84.7	112.17	772	122.4	68.8	-
3	N.H	661	34.9	98.3	919	18.4	77.1	703
4	A.T	612	35.1	81.2	755	18.2	80.1	517
5	B.N	590	38.5	100.2	620	44.5	73.8	513
6	I.M	760	42.9	77.2	224	89.2	59.3	1090
7	S.A	872	63.2	129.5	1478	45.1	67.6	380
8	M.J	1284	84.6	127.5	762	23.2	62.4	703
9	F.S	960	41.9	85.6	718	47.8	67.1	593
10	W.G	1234	91.9	87.4	696	71.2	71.6	608
11	W.K	824	84.5	111.4	1857	33.1	60.9	513
12	S.M	1550	114.42	128.42	629	58.5	61.5	345
	Mean	890	61.35	101.3	829	54.2	68.3	596
	SEM	64.6	6.7	7.100	71.07	9.7	1.9	67.9

(B)

FFA *	Ketone bodies ** acetoacetate + hydroxybutyrate umol/L	Lactate *** umol/L	Pyruvate *** umol/L	Glucose *** mg/100 ml	Cortisol *** n mol/L
340-725	18-78 + 58-170	550-1600	34-102	70-100	180-560

References of adult normal values:

- * FFA : Duncombe (1964); Clinica, Chimica Acta 9:122.
- ** Ketone bodies: Bergmeyer and Brent (1965). Enzymol Biol Clin 5: 65.
- *** Lactate: Hohorst-Bergmeyer, (1963). New York, Academic Press, p. 266.
- ** Pyruvate: Williamson, Mellanby and Krebs (1962); Biochemical J. 82: 90.
- *** Glucose: Schmidt. (1961); Klin. Wschr; 39:1244.
- *** Cortisol: Gore and Lester (1975): Annals of Clinical Biochemistry; 12:150.

DISCUSSION:

Pregnant women appear to have higher plasma FFA concentrations and lower blood glucose than the reference values of the non-pregnant individuals after an overnight fast. The result is in agreement with the observations of other workers. Fioretti 1970 have reported mean plasma FFA concentration of $(564 \pm 24 \text{ umol/L})$ in pregnant subjects following an overnight fast, Fairweather 1971 found FFA values of $(825 \pm 75 \text{ umol/L})$ in pregnant women.

Certainly the high initial fasting FFA levels in the pregnant subjects after an overnight fast can not be attributed to technical artefact. Since, the method of estimation of plasma FFA used in this work was the colorimetric method, similar to that used in previous studies. Furthermore, that, the precision of this method is also comparable to that which employ titrimetric technique.

Also, the high initial plasma FFA concentrations in the pregnant women can not be attributed in most cases to an absence of insulin. Although measurement of plasma insulin have not been done in this study, but previous studies have shown that, insulin levels during pregnancy were not significantly altered from the mean values of the non-pregnant women (Taylor, Modie, Agbedona and Akande, 1978). Some other factors, such as increased plasma levels of pituitary fat mobilizing substances and placental hormones

or impaired fatty acid re-esterification as suggested by (Fioretti, Genazzani, Aubert, Gragnoli and Pupillo, 1970) may cause the high plasma FFA concentrations observed in the pregnant women.

The importance of increased FFA levels during pregnancy may be mainly to spare glucose utilization for foetal development. The pregnant subjects also showed a tendency toward lower blood glucose values and this in turn may emphasize increased glucose utilization for vital processes.

CHAPTER 4

METABOLIC AND HORMONAL CHANGES IN RESPONSE
TO LABOUR, COMPARATIVE STUDIES BETWEEN
OBESE AND NORMAL WEIGHT SUBJECTS.

INTRODUCTION:

In the past decade while considerable interest and effort have been devoted to increasing our understanding of energy metabolism during labour in normal subjects, little information is available, however on the change during labour in patients with altered metabolic and nutritional situations such as obesity.

A number of metabolic and hormonal abnormalities have been reported to exist in human obesity.

Elevated fasting plasma FFA concentrations (Opie and Walfish, 1963) and also triglycerides (Albrink and Meigs, 1965) which do not change significantly during short period of starvation, have been observed.

The development of starvation ketosis may be slower in obesity (Kekwick, Pawan and Chalmers, 1959) and (Gorden, Brandabur, Gee and Rankin, 1962) has claimed that obese subjects oxidise glucose, FFA and ketone bodies at a slower rate than normal.

The fasting concentration of insulin is elevated in obesity (Bagdade, Bierman and Porte, 1967) and although the secretion of insulin in response to glucose load is greater than the lean subject (Karam, Grodsky and Forsham, 1963) glucose tolerance may be decreased (Butterfield, Hanley and Whichelow, 1965). These changes in obesity may

result in abnormal energy metabolism during labour. Labour is known to accelerate metabolic and hormonal activity. Human subjects are not, however homogenous for their degree of metabolic responses to labour but may varies considerably. In order to investigate the range in human subjects, I have studied normal and obese subjects during the course of labour.

METHOD:

Twenty eight (28) pregnant subjects were included in this study. Twenty two (22) of them were of normal body weight and six (6) were with marked obesity as judged from their ht., wt., and reciprocal ponderal index table 4.1 .

The subjects of both groups were at 38-40 weeks of pregnancy. No one suffered from any metabolic or hormonal disorder and pregnancy was uncomplicated in all of them. The subjects were admitted to the labour ward in spontaneous labour, and blood samples were taken from a forearm vein as follows:

- 1 - At the begining of the first stage of labour and while the subjects were comfortably rested in the labour room.
- 2 - In the second stage of labour (most of the specimens at this stage were taken at the momment of delivery except in few cases where 2.5 min. before delivery were allowed for technical reasons.

3 - 30 min. after delivery.

The blood samples were collected in a proper container and were treated as previously described page 19-20 and were analysed for glucose, pyruvate, lactate, FFA, glycerol, ketone bodies and cortisol.

Table 4.1

A -- normal weight

No.	Subjects	Age Yr	Weight kg	Height cm.	Duration from Admiss- ion to labour room to delivery hr / min	Reciprocal Ponderal index	over - weight %
1	F.A	21	70	160	5.30	38.8	125
2	R.F	25	76	166	6.00	39.2	113
3	N.M	28	60	162	4.40	41.4	100
4	S.A.A	33	62	160	5.00	40.44	101
5	A.M	22	62	160	3.40	40.1	103
6	A.G	30	64	155	3.00	38.75	110
7	N.J	26	68	162	4.30	39.7	109
8	A.I	24	73	160	4.00	38.8	118
9	F.A	37	65	160	2.30	39.8	112
10	H.J	34	55	159	4.30	41.6	100
11	B.I	37	75	165	3.00	39.13	112
12	I.N	15	60	156	4.20	39.8	119
13	R.H.S	21	62	160	3.00	40.1	110
14	A.A	20	62	158	4.30	39.9	112
15	I.G	19	60	160	3.20	40.8	107
16	F.A.L	18	62	155	3.50	39.1	119
17	S.M	23	55	155	4.35	39.81	104
18	N.H	28	68	158	5.30	38.7	117
19	S.L	23	65	156	4.30	38.8	120
20	A.M.R	26	60	158	4.00	39.95	103
21	M.A.H	19	63	162	4.30	40.3	109
22	N.H.W	19	70	156	3.00	38.6	125
	Mean	24.95	64.6	159.5	4.20	39.7	112.1
	SEM	1.315	1.283	0.643	0.402	0.19	1.608

Table 4.1

B - Overweight.

No.	Subjects	Age Yr	Weight Kg	Height cm.	Duration from admission to labour room to delivery hr/min	Reciprocal ponderal index	Over - weight %
1	N.A.M	37	108	164	11.0	34.4	166
2	A.A.H	20	89	158	3.00	35.4	168
3	B.K	27	98	160	5.30	34.7	170
4	H.S	21	87	158	5.30	35.6	164
5	S.A.M	18	99	156	5.30	33.7	187
6	N.A	27	99	160	4.00	34.5	167
	Mean	25	96.6	159.3	5.58	34.7	170.3
	SEM	3.032	2.798	1.208	1.051	0.23	3.429

RESULTS:

The obese subjects appeared shorter than the Controls and their mean reciprocal ponderal index was smaller than of controls Table 4.1 .

Plasma FFA and blood glycerol: Fig. 4.1 , 4.2

The concentrations of plasma FFA at the beginning of first stage of labour were significantly higher in subjects with obesity compared to those of the normal body weight ($p > 0.01$).

During labour the concentrations in both groups rose in similar patterns, but in the obese subjects, the rise was more pronounced and the values at delivery were much greater than of the normal weight.

In the post delivery period, the concentrations of FFA in normal weight subjects fell towards the starting values where as in those with obesity the concentrations remained elevated so that the difference was highly significant ($p < 0.01$).

The changes in glycerol concentrations were similar to those of FFA .

Blood ketone bodies: Fig. 4.3

The concentrations of ketone bodies (Acetoacetate + 3 hydroxybutyrate) at the beginning of the first stage of labour were higher in subjects with obesity and in the

subjects of normal weight than in controls reference base line value, but they were not statistically different.

Ketone bodies concentrations rose to a maximum at delivery in the subjects of normal weight and fell afterwards, where as in the subjects with obesity the maximum occurred at 30 min. after delivery.

The values of ketone bodies in the subjects with obesity at both points i-e at delivery and 30 min afterward were significantly higher than those of normal weight ($p < 0.01$).

Blood lactate and pyruvate: Fig. 4.4 and 4.5

Blood lactate concentrations were similar at the first stage of labour and rose to a similar values at delivery. In the normal weight subjects, the concentrations returned towards the starting values by the end of the investigation, where as in the subjects with obesity, the concentrations showed a further increase and were significantly higher than in the normal weight subjects throughout the recovery period ($p < 0.01$). The changes in pyruvate concentrations were similar.

Blood Glucose: Fig. 4.6

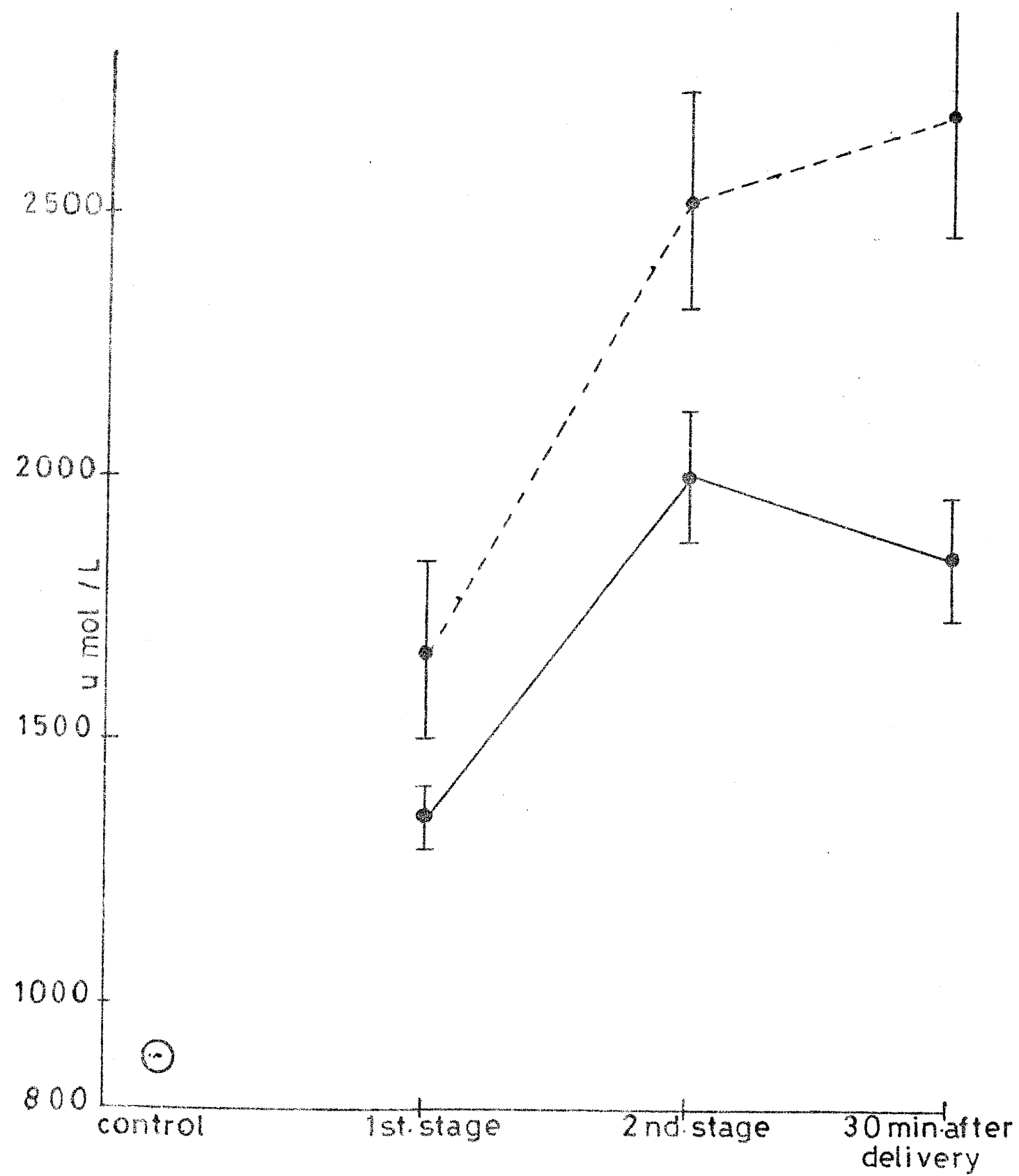
There was no difference in the starting concentrations of blood glucose in both groups. Labour caused a rise in glucose concentrations of the normal weight subjects, but in the subjects with obesity the rise was more marked at the time of delivery.

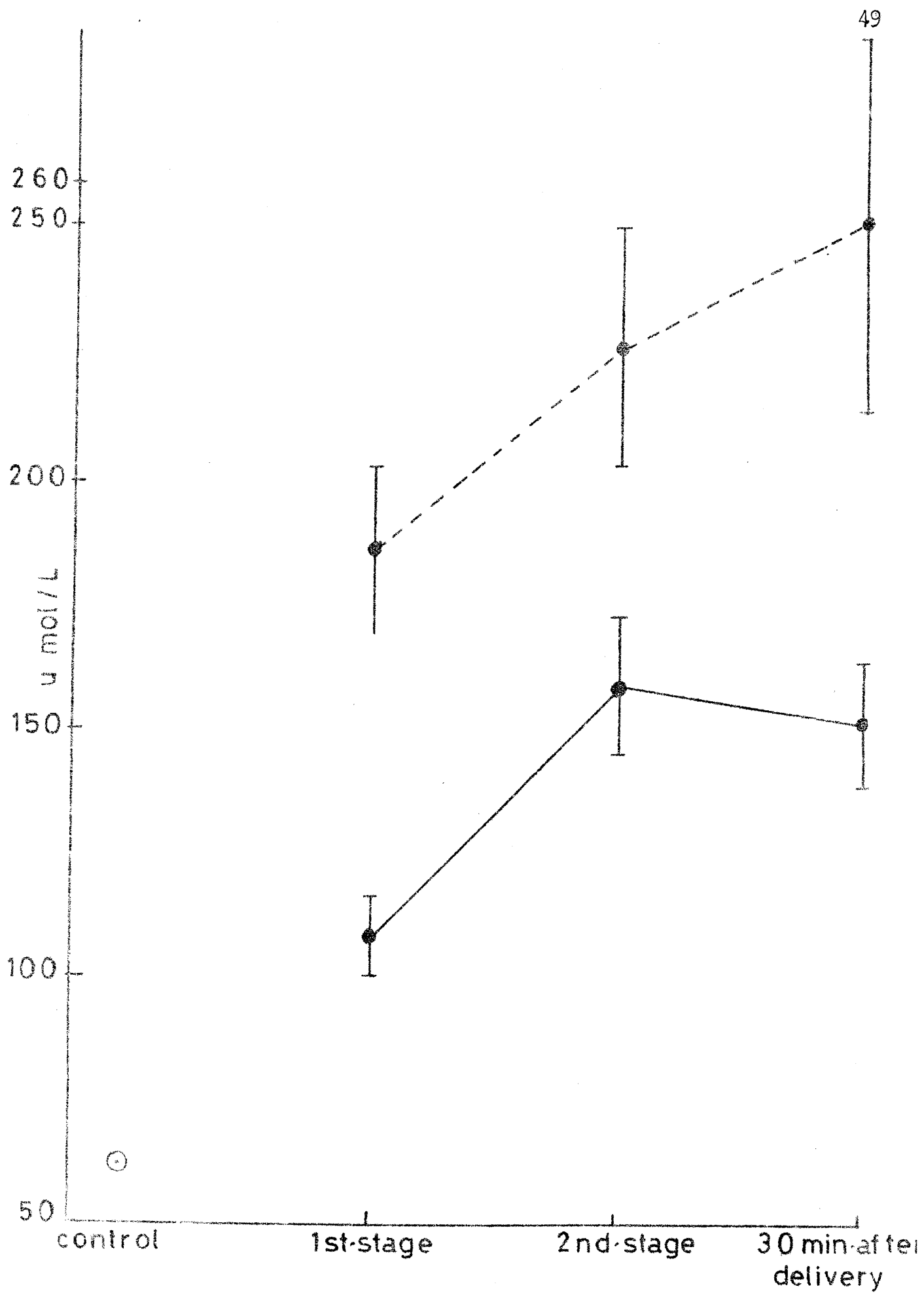
Although the levels during the whole investigation were not statistically different at any one time, in the subjects with obesity the concentrations were consistantly higher.

Plasma Cortisol: Fig 4.7

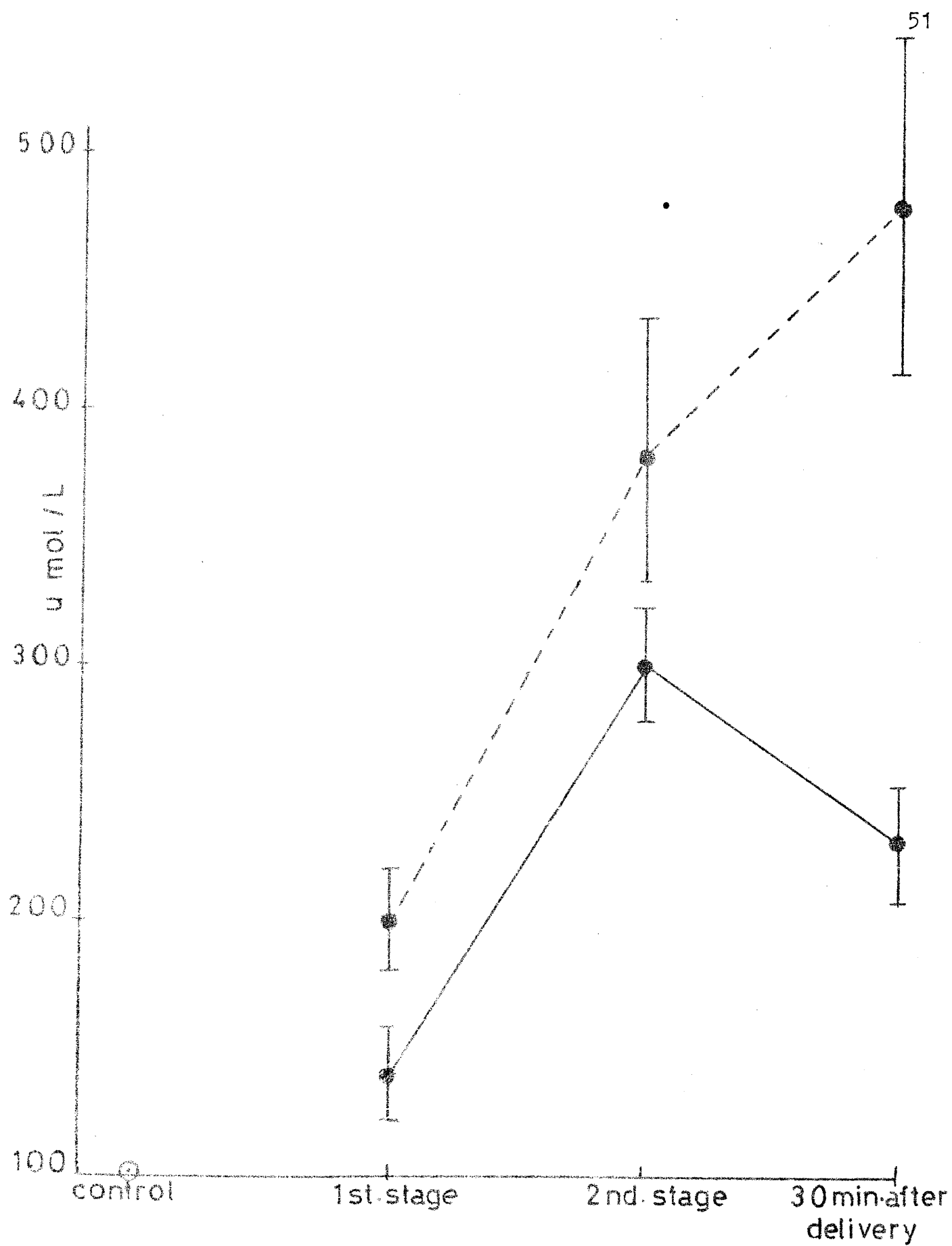
At the first stage of labour, the plasma cortisol concentrations were lower in the subjects with obesity than in the subjects of normal weight, but they were not significantly different. In both groups, the concentrations rose to achieve similar values at the delivery time. During recovery the concentrations of cortisol returned towards the starting values in the normal weight subjects where as in the subjects with obesity the concentrations remained elevated but there were no significant differences between the two groups.

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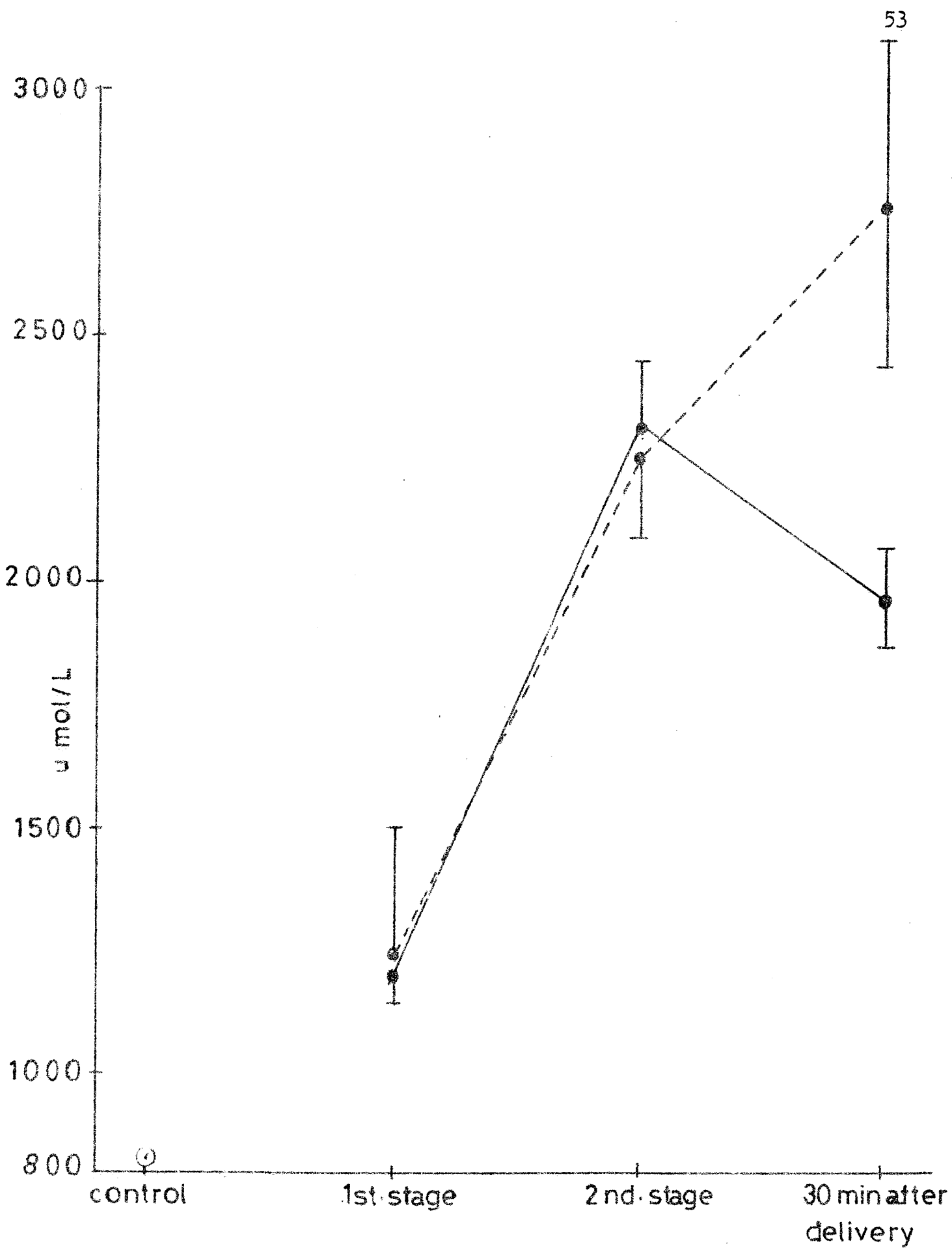


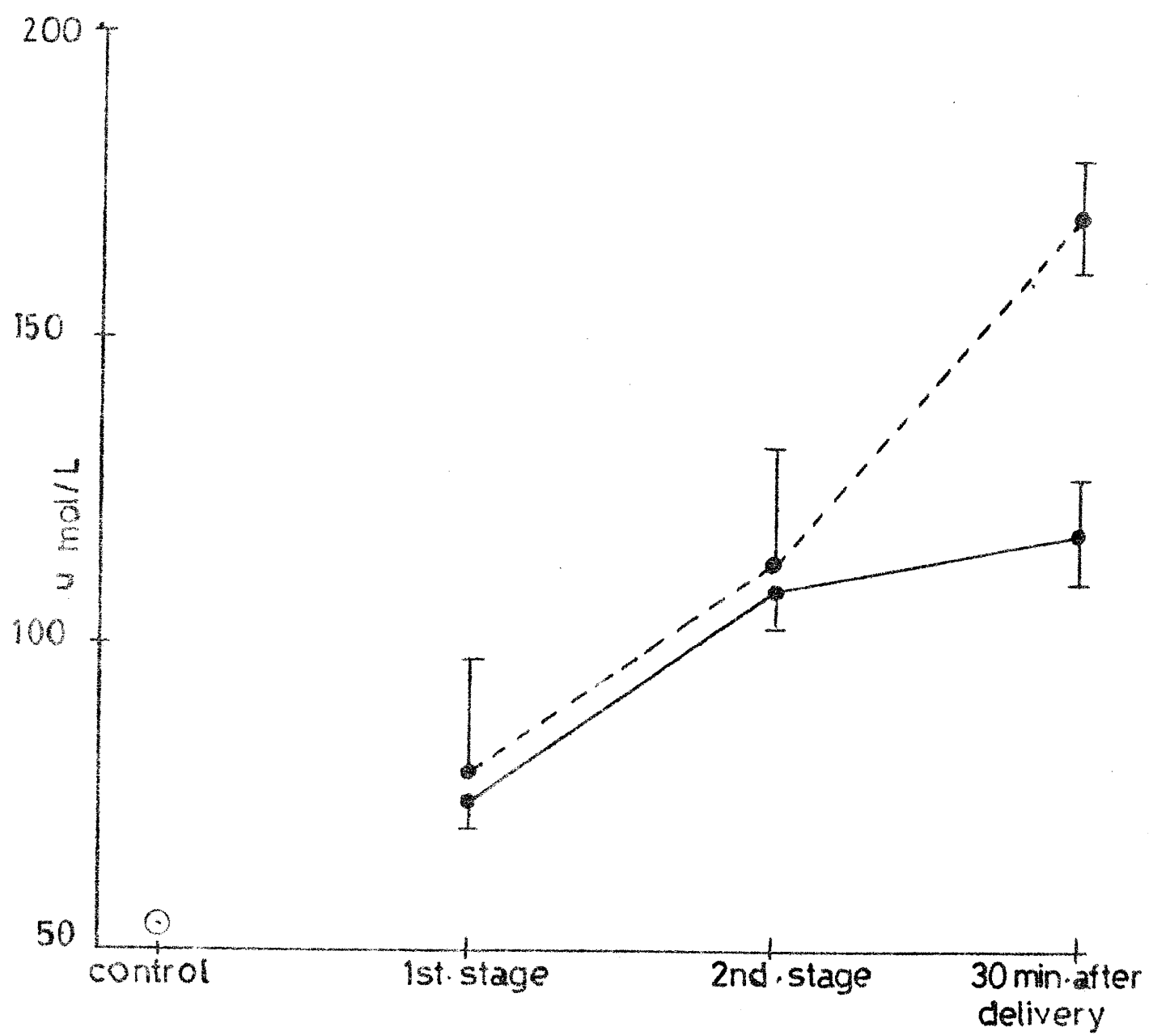


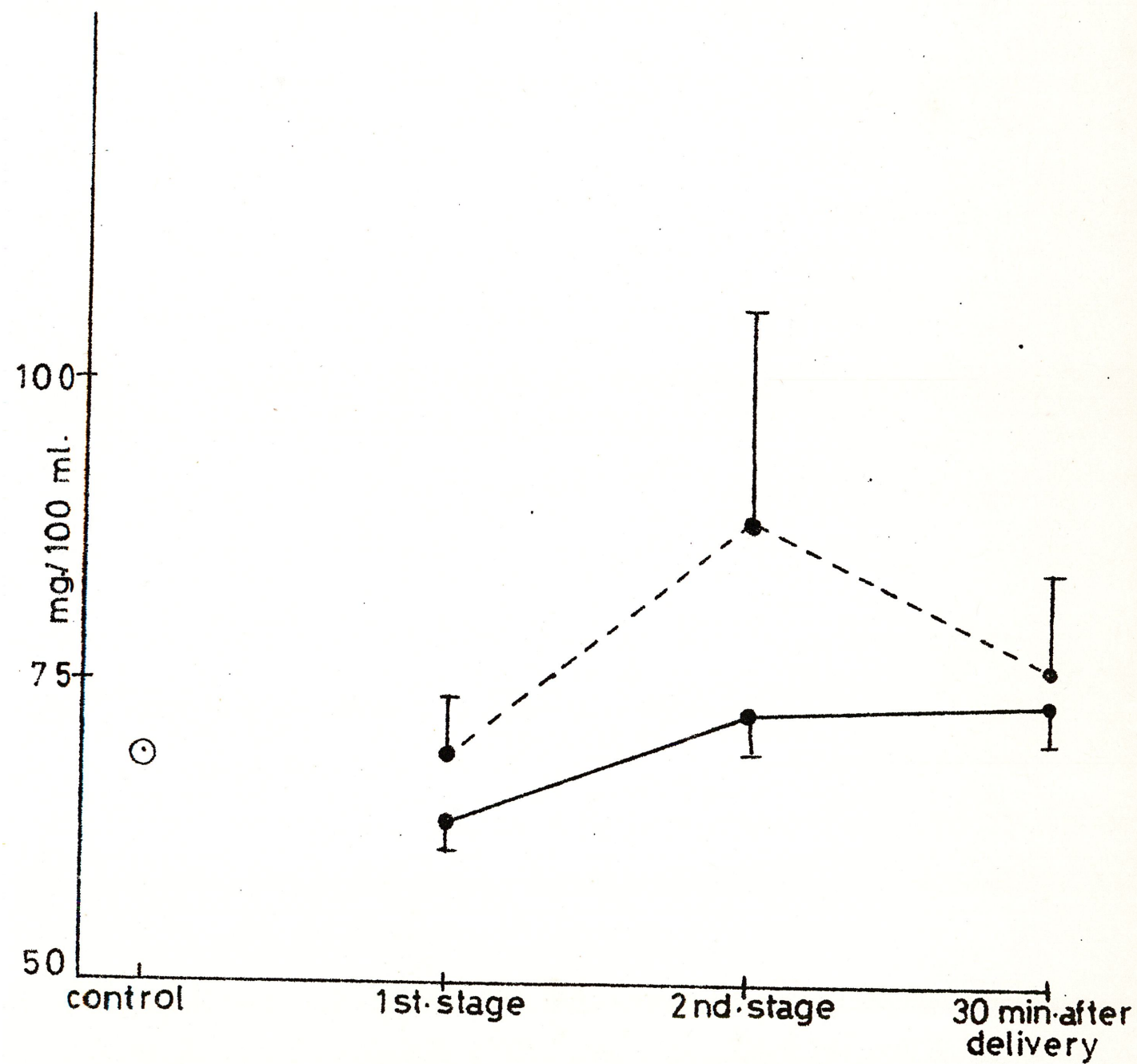
1. The first part of the paper is devoted to the study of the properties of the function $f(x)$ defined by the equation $f(x) = \int_0^x f(t) dt$. It is shown that $f(x)$ is a continuous function and that it satisfies the differential equation $f'(x) = f(x)$. The solution of this equation is $f(x) = Ce^x$, where C is a constant. The value of C is determined by the initial condition $f(0) = 1$, which gives $C = 1$. Therefore, the function $f(x)$ is $f(x) = e^x$.



1. The first part of the report is a
description of the work done during the
year. It is a summary of the work done
by the committee and is intended to be
a guide to the work of the committee.







1. The first part of the paper is devoted to the study of the properties of the function $f(x)$ defined by the equation $f(x) = \int_0^x f(t) dt$. It is shown that $f(x)$ is a constant function, and its value is determined by the initial condition $f(0) = 1$.

2. In the second part, we consider the function $g(x)$ defined by the equation $g(x) = \int_0^x g(t) dt$. It is shown that $g(x)$ is a constant function, and its value is determined by the initial condition $g(0) = 1$.

3. The third part of the paper is devoted to the study of the properties of the function $h(x)$ defined by the equation $h(x) = \int_0^x h(t) dt$. It is shown that $h(x)$ is a constant function, and its value is determined by the initial condition $h(0) = 1$.

4. In the fourth part, we consider the function $k(x)$ defined by the equation $k(x) = \int_0^x k(t) dt$. It is shown that $k(x)$ is a constant function, and its value is determined by the initial condition $k(0) = 1$.

5. The fifth part of the paper is devoted to the study of the properties of the function $l(x)$ defined by the equation $l(x) = \int_0^x l(t) dt$. It is shown that $l(x)$ is a constant function, and its value is determined by the initial condition $l(0) = 1$.

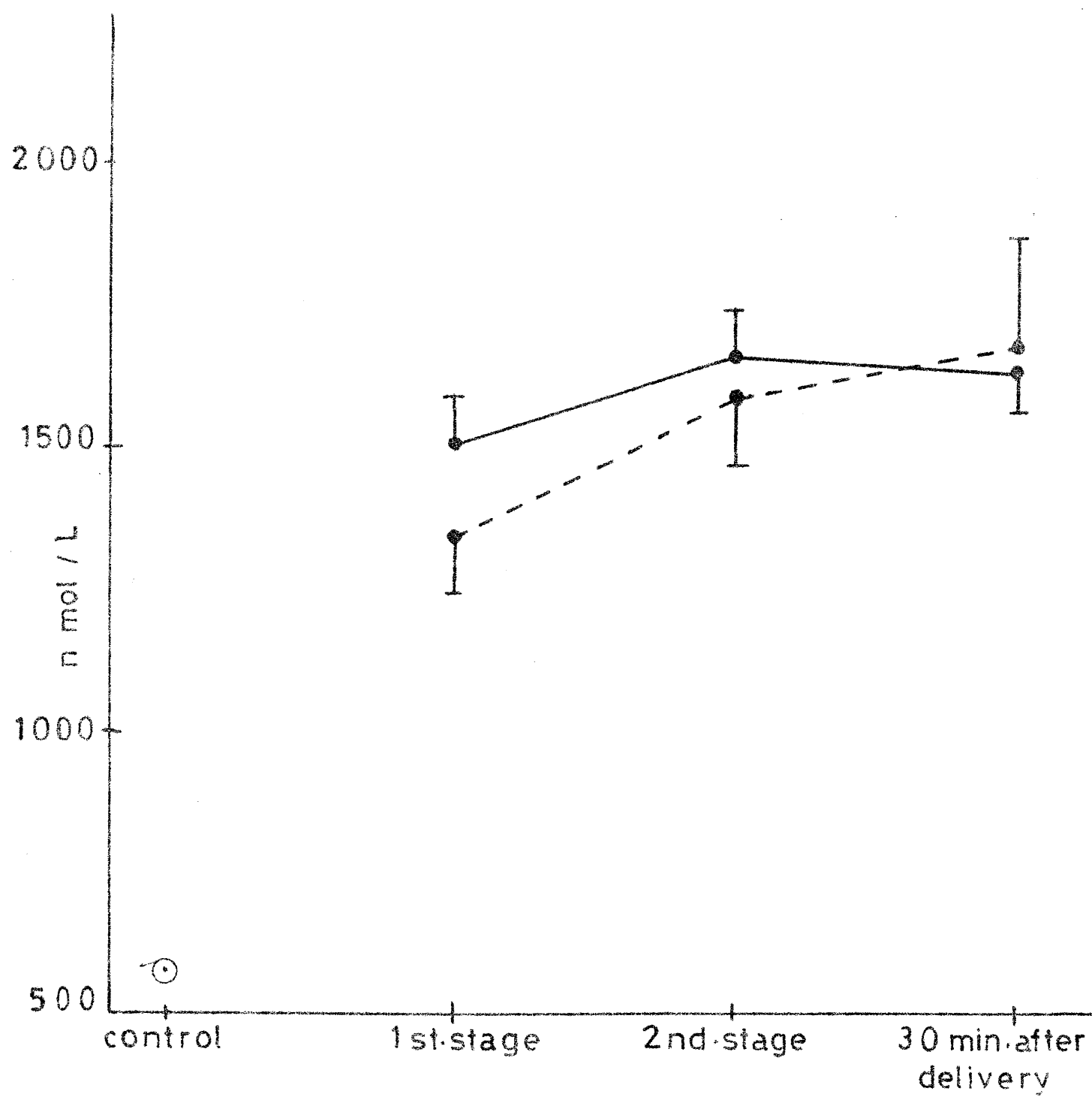
6. In the sixth part, we consider the function $m(x)$ defined by the equation $m(x) = \int_0^x m(t) dt$. It is shown that $m(x)$ is a constant function, and its value is determined by the initial condition $m(0) = 1$.

7. The seventh part of the paper is devoted to the study of the properties of the function $n(x)$ defined by the equation $n(x) = \int_0^x n(t) dt$. It is shown that $n(x)$ is a constant function, and its value is determined by the initial condition $n(0) = 1$.

8. In the eighth part, we consider the function $o(x)$ defined by the equation $o(x) = \int_0^x o(t) dt$. It is shown that $o(x)$ is a constant function, and its value is determined by the initial condition $o(0) = 1$.

9. The ninth part of the paper is devoted to the study of the properties of the function $p(x)$ defined by the equation $p(x) = \int_0^x p(t) dt$. It is shown that $p(x)$ is a constant function, and its value is determined by the initial condition $p(0) = 1$.

10. In the tenth part, we consider the function $q(x)$ defined by the equation $q(x) = \int_0^x q(t) dt$. It is shown that $q(x)$ is a constant function, and its value is determined by the initial condition $q(0) = 1$.



DISCUSSION:

The results of this study demonstrate that during the course of labour, progressive increase in the concentrations of glycerol, FFA and more strikingly ketone bodies occur in obesity. The plasma concentration of FFA at any given time is the result of the amount that is mobilized from adipose tissue minus the amount that is utilized. It is generally accepted that the rate of utilization of FFA by body tissues, is to a large extent dependent upon the blood concentration of FFA. Thus, the progressive rise in plasma FFA during labour are most likely due to an increase in the rate of fat mobilization.

In this study the concentrations of both glycerol and plasma FFA were higher in the subjects with obesity. This suggest that they had a greater degree of fat mobilization. The percentage change of plasma FFA at delivery were, however, similar in both groups, but the concentrations at the 1st stage and at delivery were higher in the subjects with obesity.

It therefore appears that, during labour, the subjects with obesity have the ability to mobilize and utilize more fat than the normal weight subjects.

The obese women also showed a greater blood glucose values throughout and this may be further evidence for the greater reliance on fat as fuel for energy during labour in obesity.

As the concentrations of blood ketone bodies rose during labour, there is probably an imbalance between production and utilization. After delivery, however, when the need for fuel decreases, there is a rise in the ketone bodies concentrations.

During the course of labour, the striking rise in the concentration of ketone bodies was not previously reported, although such changes is known to occur after exercise (Johnson, Walton, Krebs and Williamson 1969 ; Johnson and Walton 1972) and this probably is due to accumulation of acetyl CoA.

The much greater rise during labour and after delivery in subject with obesity may reflect a decrease in their ability to oxidise Acetyl CoA through the citric acid cycle (Gordon 1960).

The impaired carbohydrate utilization and also insulin resistance which have been reported in obesity (Karam, et al 1963) would also tend to increase ketone bodies production.

In this study, it was shown that the increase in maternal plasma FFA which occur during labour is associated with arise in the concentration of blood ketone bodies . Despite increases in maternal FFA, however, transplacental passage was shown to be limited (Koren, Shafrin, 1964) and steady state concentration of FFA in fetal circulation remain unchanged (Dahlquist, Persson and Persson 1972).

Ketone bodies have been shown to cross the placenta readily, thereby providing possible substrate for foetal utilization as an alternative fuel during labour particularly when other fuels are needed by the mother.

More than two decades ago, it was shown that ketone bodies could be readily oxidised by adult liver, working muscle and brain (Krebs 1966). It remain to be demonstrated whether adult potentialities for ketone utilization is operative in various foetal tissues.

Nonetheless, it is likely that some of the increase in foetal liver glycogen which was reported (Goodner, and Thompson, 1967) may reflect at least in part some sparing of foetal glucose via the increased availability of oxidisable ketones.

Blood lactate and pyruvate concentrations are known to be increased during labour (Low, Pancham, Worthington and Boston, 1974 ; Kashyap, Sivasambo, Sothy, Cheah and Gartside, 1976). In this study I report similar changes in both groups (normal and obese subjects) because lactate and pyruvate are known to increase after stress or muscular activity as a result of muscle glycolysis which exceeds removal mechanism (Hermansen 1971). The concentrations of pyruvate and lactate in obese subjects during labour and after delivery are greater than of normal subjects because the increased rate of fat oxidation

increases Acetyl CoA levels which blocks pyruvate oxidation resulting in the accumulation of both pyruvate and lactate (Garland and Randle, 1964).

In this study there was no difference in the plasma cortisol response to labour between the two groups. This suggest that during labour almost all subjects were under similar stressful work.

It further suggest that the observed metabolic differences between the two groups, during labour were true metabolic changes related to obesity and not to the degree of stress.

CHAPTER 5

METABOLIC AND HORMONAL CHANGES DURING LABOUR,
COMPARATIVE STUDIES BETWEEN SPONTANEOUS
LABOUR AND OXYTOCIN INDUCED LABOUR.

INTRODUCTION:

In the previous studies on the utilization of metabolic fuels during spontaneous labour described in chapter 4 . It was observed that obese subjects although having relatively high blood glucose throughout the process of labour, they were able to mobilize more fat and had also a marked degree of ketosis.

These results indicate that, ketosis in response to labour may arise from an excessive use of fat over-carbohydrate as an energy source.

The suggestion was also made that excessive fat metabolism might be a key factor underlying the decreased glucose tolerance usually seen in pregnancy.

Exogenous glucose given either orally or by intravenous infusion is known to stimulate insulin secretion and consequently may limit fat mobilization and enhances fat deposition. In this situation, whether, the subjects undergoing labour are able to mobilize and oxidise fat it remain to be explored. An opportunity of investigating the role of exogenous glucose infusion on metabolism in response to labour, is provided by studying a group of subjects undergoing labour induced with oxytocin in 5% glucose solution.

METHOD:

Twenty eight (28) pregnant subjects were included in this study and they were divided into two groups Table 5.1 . The first group comprising (22) subjects in whom labour was started spontaneously whereas the second group comprising (6) subjects in whom labour was induced by oxytocin infusion.

Synthetic oxytocin 2-6 IU, mixed with 5% glucose solution was infused I.V at a speed varied from 15-60 drops/min for a period from the start of induction and until 15 min after the expulsion of placenta. Indication for induction was in the majority of cases assumed postmaturity and in one case was Rh. immunization. Pregnancy was uncomplicated in all the subjects of this study and they were all considered healthy in respect to their metabolic conditions. The neonates were all in good conditions as judged by apgar scoring.

Blood samples were taken as previously described in chapter 2 and were analysed for glucose, FFA, glycerol, lactate, pyruvate, ketone bodies and cortisol.

Table 5.1

(A)

No.	Subjects	Age Yr	Weight Cm	Height Kg	Duration from admission to labour room to delivery hr / min	Reciprocal ponderal index	Overweight %
1	F.A	21	70	160	5.30	38.8	125
2	R.F	25	76	166	6.00	39.2	113
3	N.M	28	60	162	4.40	41.4	100
4	S.A.A	33	62	160	5.00	40.1	101
5	A.M	22	62	160	3.40	40.44	103
6	A.G	30	64	155	3.00	38.75	110
7	N.J	26	68	162	4.30	39.75	109
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18	N.H	28	68	158	5.30	38.7	117
19	S.L	23	65	156	4.30	38.81	120
20	A.M.R	26	60	158	4.00	39.3	103
21	M.A.H	19	63	162	4.30	40.3	109
22	N.H.W	19	70	162	3.00	38.6	125
	Mean	24.95	64.6	159.3	4.20	39.7	112.1
	SEM	1.315	1.28	0.643	0.402	0.19	1.608

Table 5.1

(B)

No.	Subjects	Age Yr	Height Cm	Weight Kg	Time interval from start of labour to delivery hr / min	Quantity of drip solution ml	Reciprocal ponderal index	Over- weight %
1	S.K	28	161	75	5.30	800	38.18	120
2	A.A.K	22	163	79	11.00	1300	37.99	116
3	R.H.S	20	160	74	7.00	650	38.11	123
4	J.K	30	158	63	7.30	800	39.7	112.5
5	B.A	20	160	70	5.00	450	38.8	116.6
6	F.I.M	21	158	66	5.30	600	38.35	115.8
	Mean	23.5	160	71.1	7.08	857	38.47	117.316
	SEM	1.784	0.774	2.43	0.921	119.4	0.223	1.48

RESULTS

Plasma FFA: Fig. 5.1

Plasma FFA concentrations at the first stage of labour were significantly lower in subjects in whom labour was induced by oxytocin than in those of spontaneous labour ($p < 0.01$). During labour in both groups, FFA values rose in similar patterns but the values at delivery were significantly lower in subjects in whom labour was induced; Nevertheless the percentage change over the starting values were similar in both groups.

Blood Glycerol: Fig. 5.2

At the first stage of labour, the concentrations of blood glycerol were similar in both groups. Labour caused an increased in glycerol concentrations to similar values at delivery in both groups, but the rate of increase was much faster in the subjects in whom labour was induced by oxytocin.

Blood Ketone bodies: Fig. 5.3

At the first stage of labour, the concentrations of total ketone bodies (acetoacetate + 3 hydroxybutyrate) were similar in both groups. Labour caused a rise in ketone bodies concentrations by about 62% from the starting levels in the subjects in whom labour was induced, but the subjects in spontaneous labour showed a greater

rise (115%) above the starting values; In the post delivery period, concentrations of blood ketone bodies declined in both groups.

Blood Pyruvate: Fig 5.4

Blood pyruvate concentrations were similar at the first stage of labour in the two groups and rose in a similar pattern to a maximum values at delivery, but the values were significantly higher in the subjects of induced labour than in subjects of spontaneous labour. In post delivery period, pyruvate concentrations remained elevated in both groups.

Blood Lactate: Fig. 5.5

Initial concentrations of blood lactate were similar in the two groups. Labour increased the values of lactate in both groups, but the increase was larger in the subject in whom the labour was induced, so that at delivery the difference between the two groups was highly significant ($p < 0.01$). After delivery, the concentrations decreased faster in case of oxytocin when compared with those of spontaneous delivery but in both groups the values at this point still significantly higher than their own initial values.

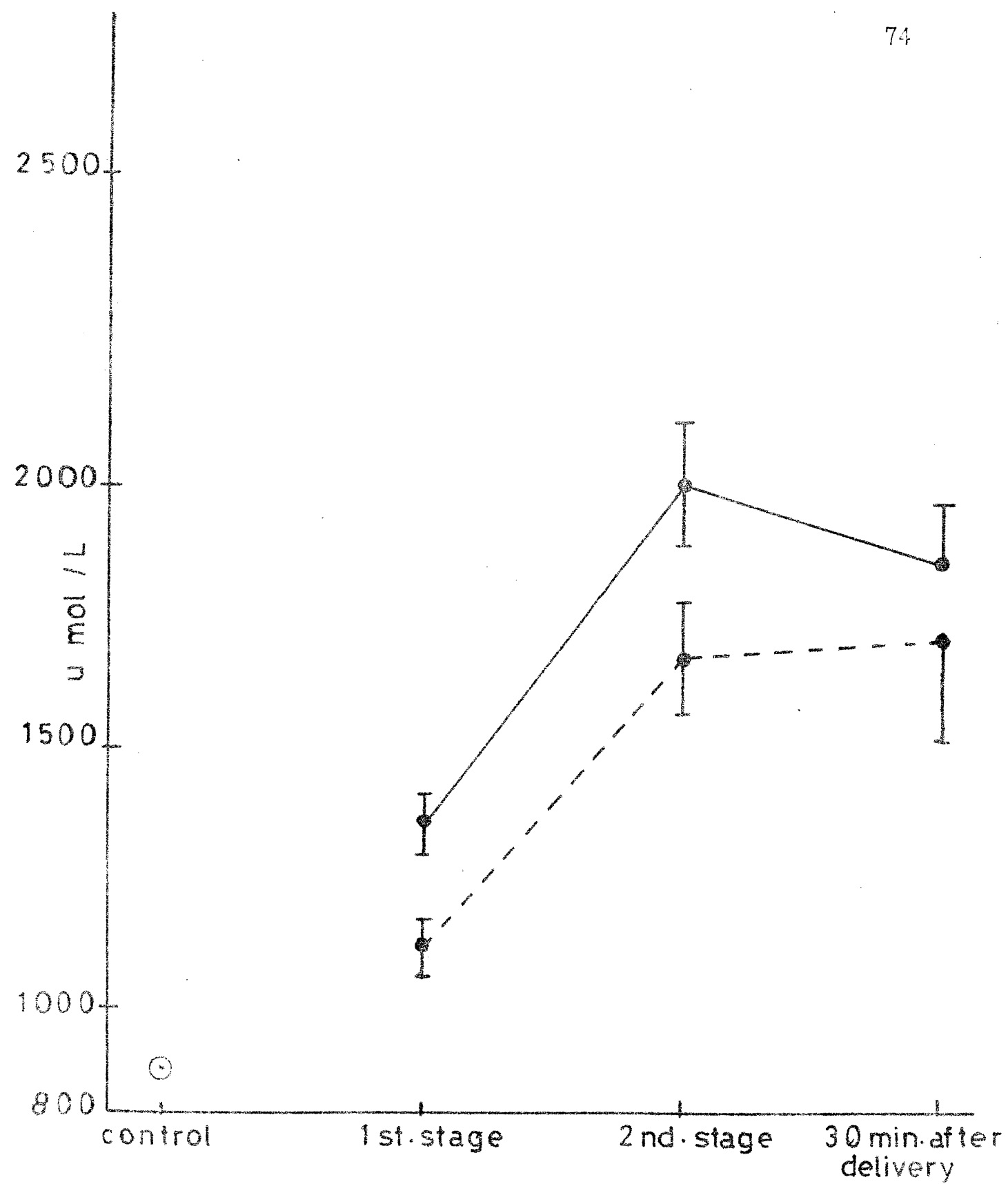
Blood Glucose: Fig. 5.6

At the first stage of labour and at delivery, the glucose levels in patients undergoing induced labour were greater than those in the group undergoing spontaneous labour. After delivery the glucose levels decreased in the group in whom labour were induced while the levels in group undergoing spontaneous labour were slightly increased.

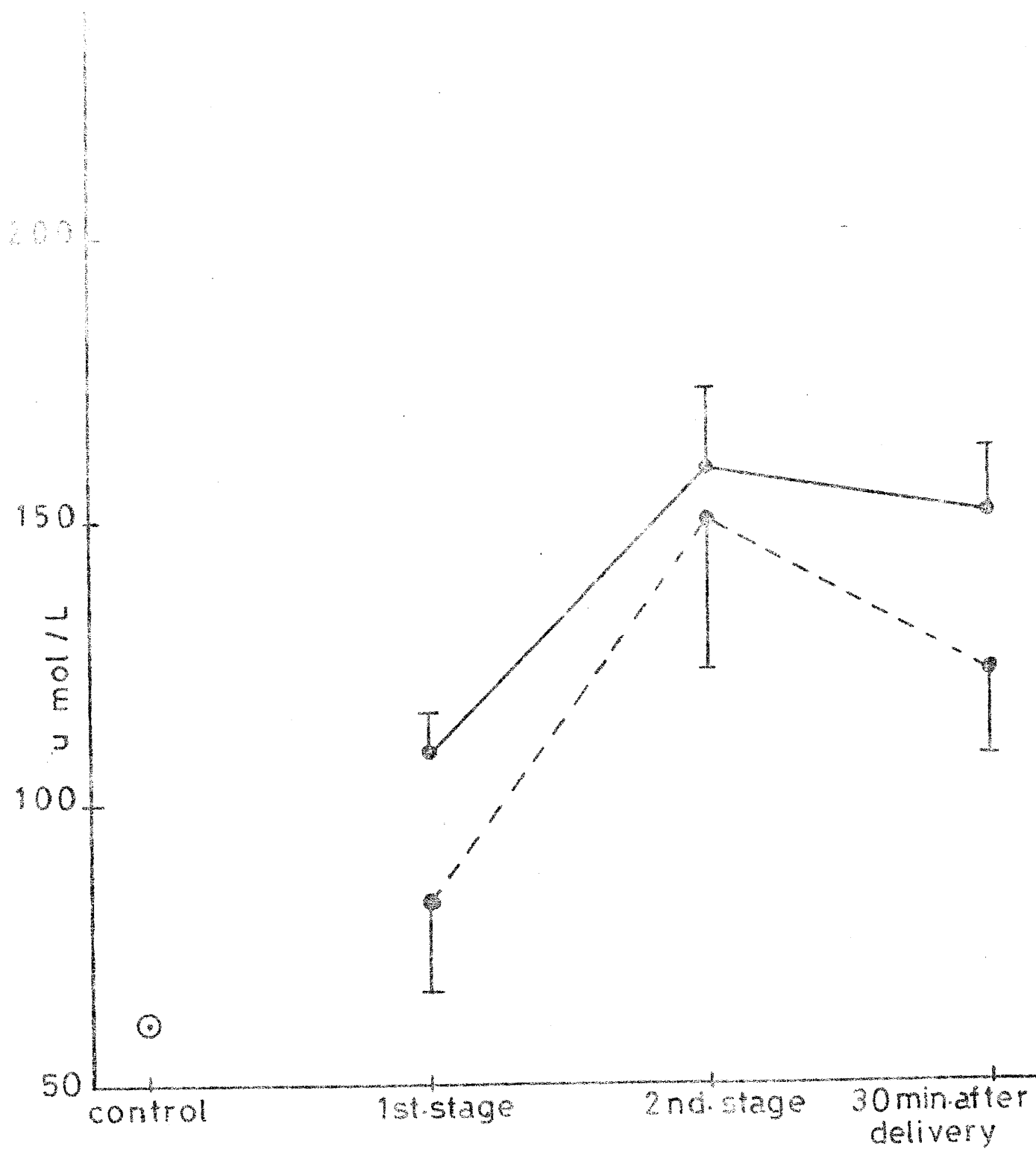
Plasma Cortisol: Fig. 5.7

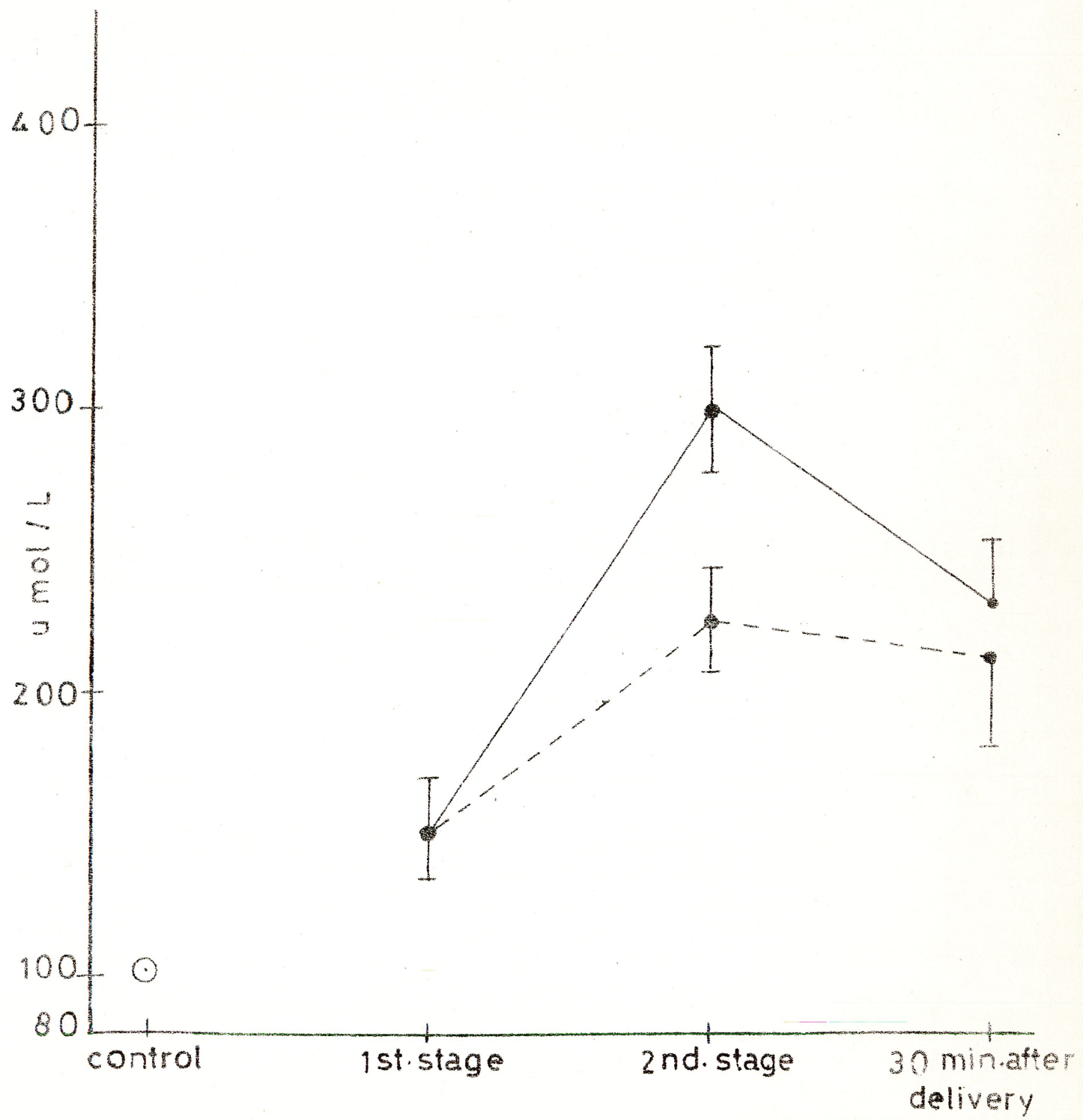
The intial levels of plasma cortisol in both groups were similar, but at delivery, in case of induced labour, the elevation was higher than those in spontaneous labour. After delivery in both groups, the levels were decreased but the levels in induced labour were still higher than those in spontaneous labour.

1. The first part of the paper discusses the importance of the study of the history of the English language. It is argued that the study of the history of the English language is essential for a full understanding of the language and its development. The paper then discusses the various factors that have influenced the development of the English language, including the influence of other languages, the influence of social and cultural changes, and the influence of technological advances.



1. The first part of the paper discusses the importance of the study of the history of the English language. It is argued that the study of the history of the English language is essential for a full understanding of the language and its development. The paper then goes on to discuss the various factors that have influenced the development of the English language, such as the influence of other languages, the influence of social and cultural changes, and the influence of technological advances.





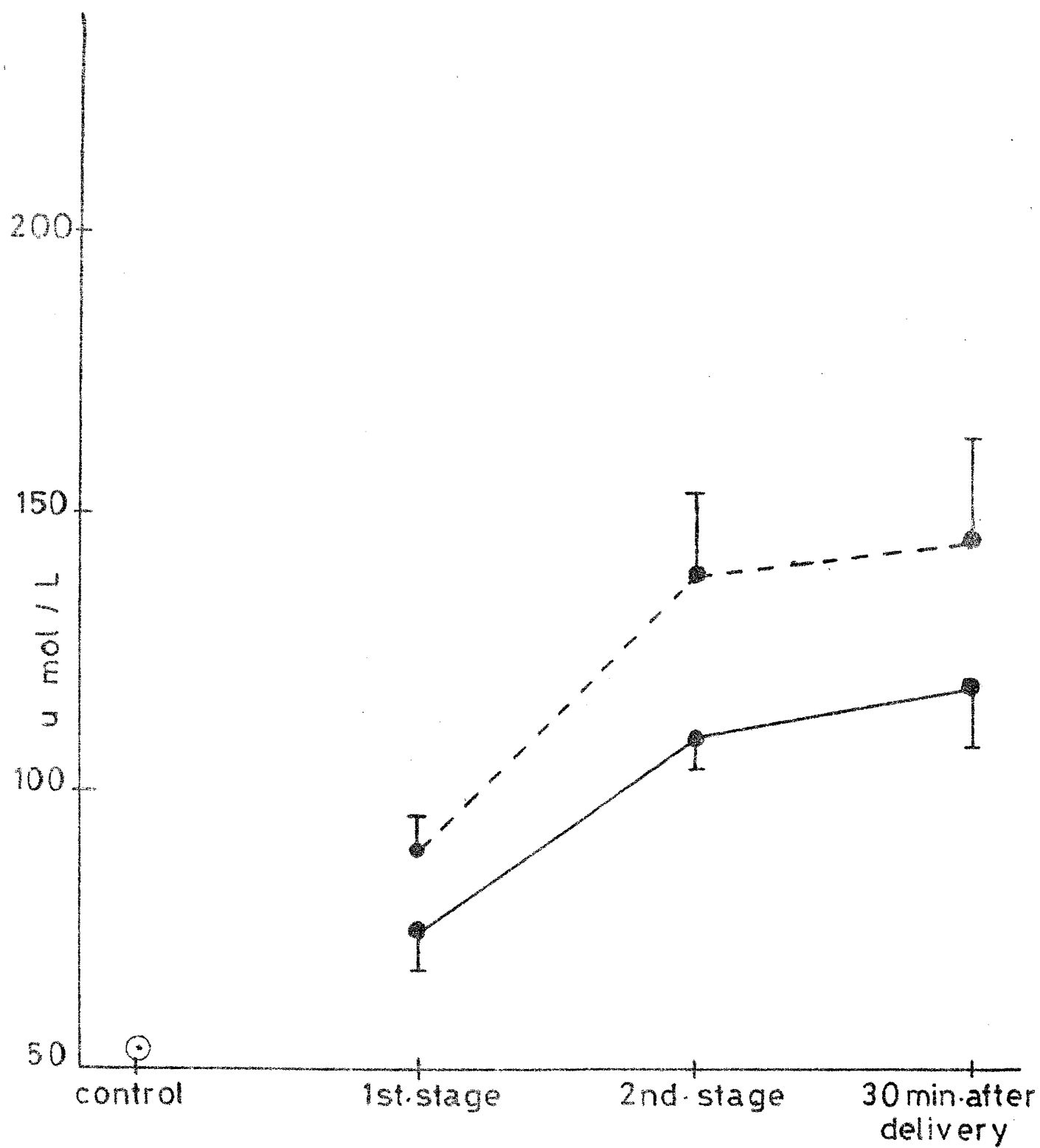
1. The first part of the document is a letter from the President of the United States to the Congress, dated January 3, 1862.

2. The second part is a report from the Secretary of the Treasury, dated January 3, 1862.

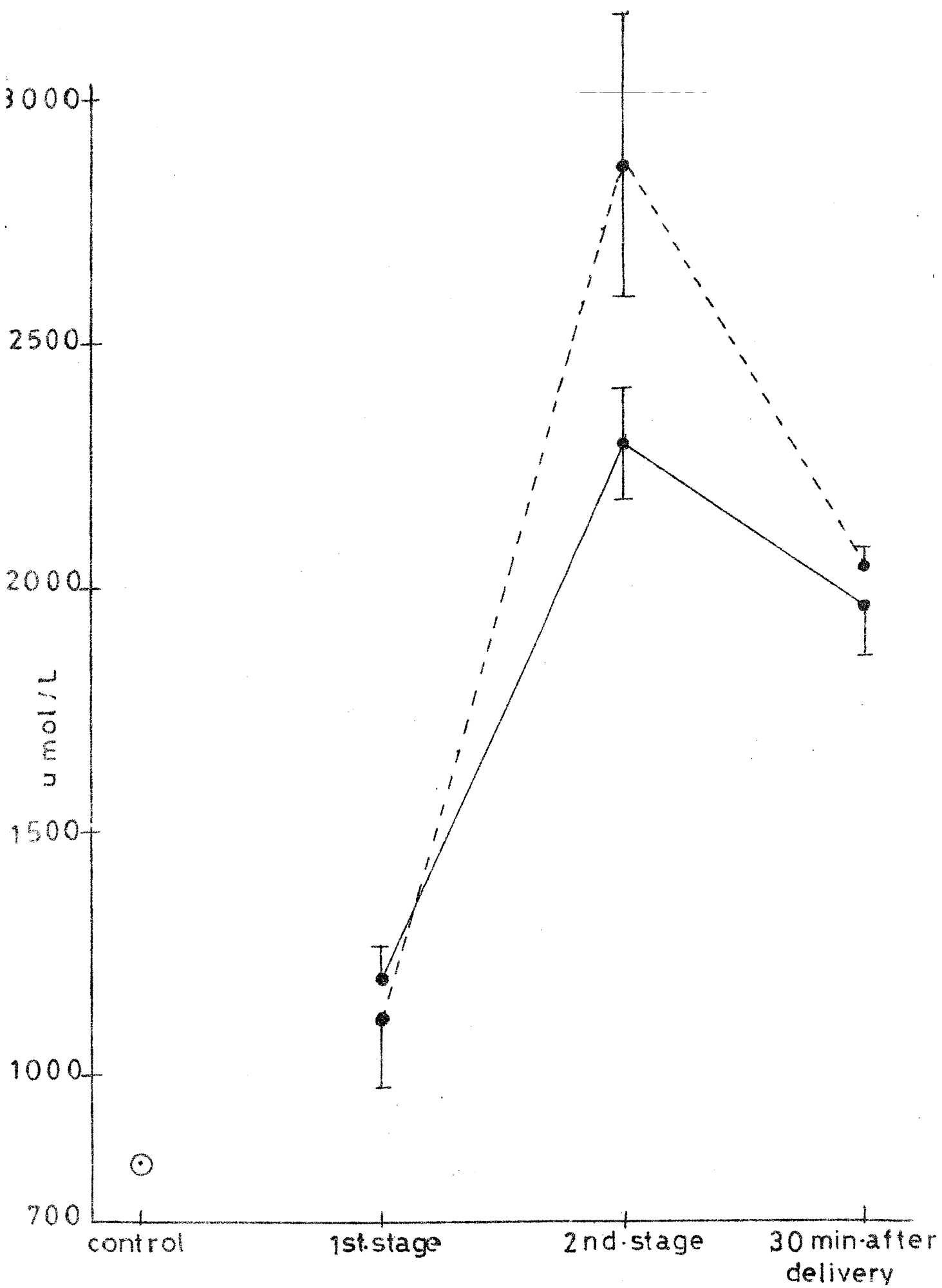
3. The third part is a report from the Secretary of the Interior, dated January 3, 1862.

4. The fourth part is a report from the Secretary of the Navy, dated January 3, 1862.

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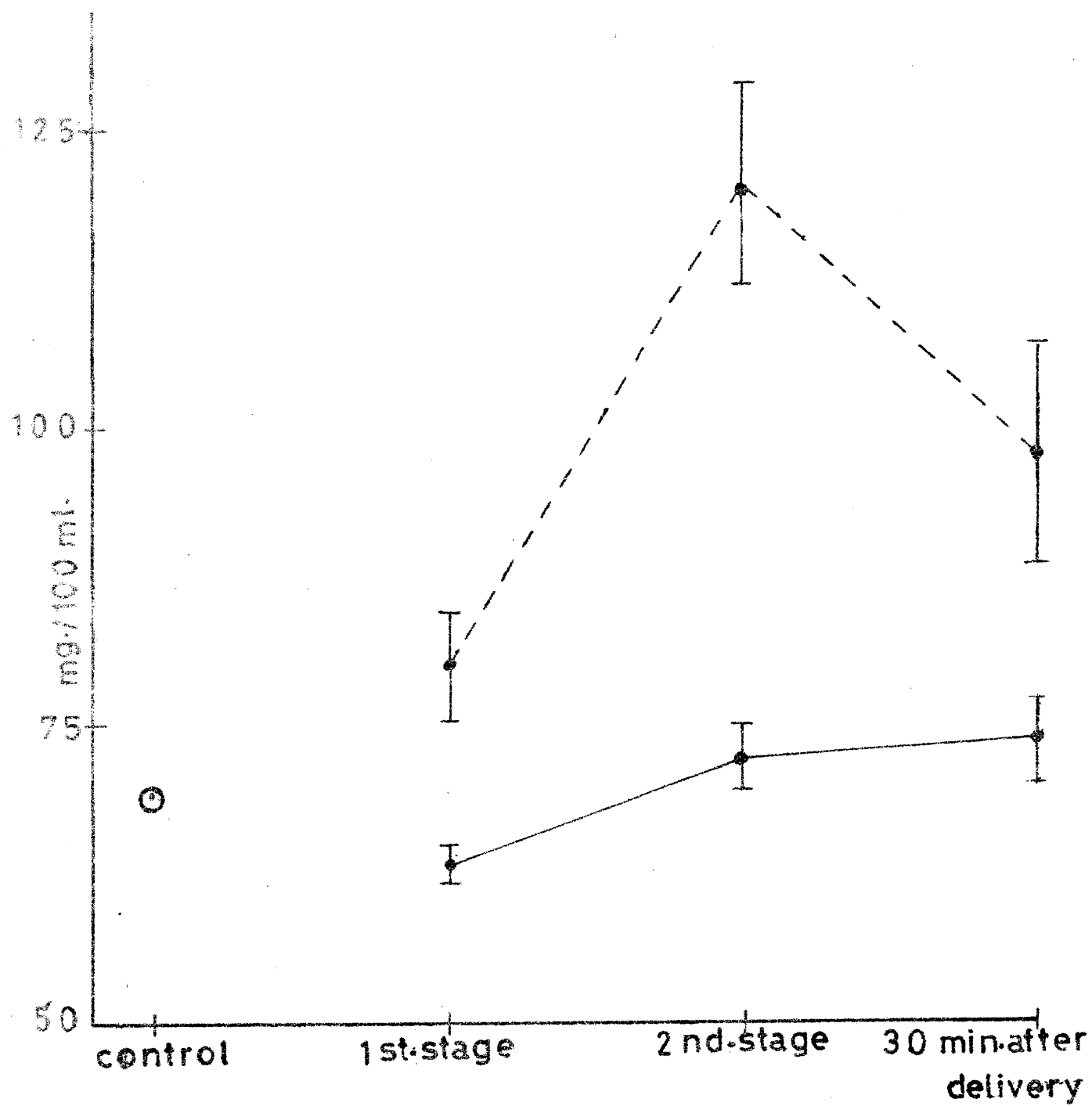
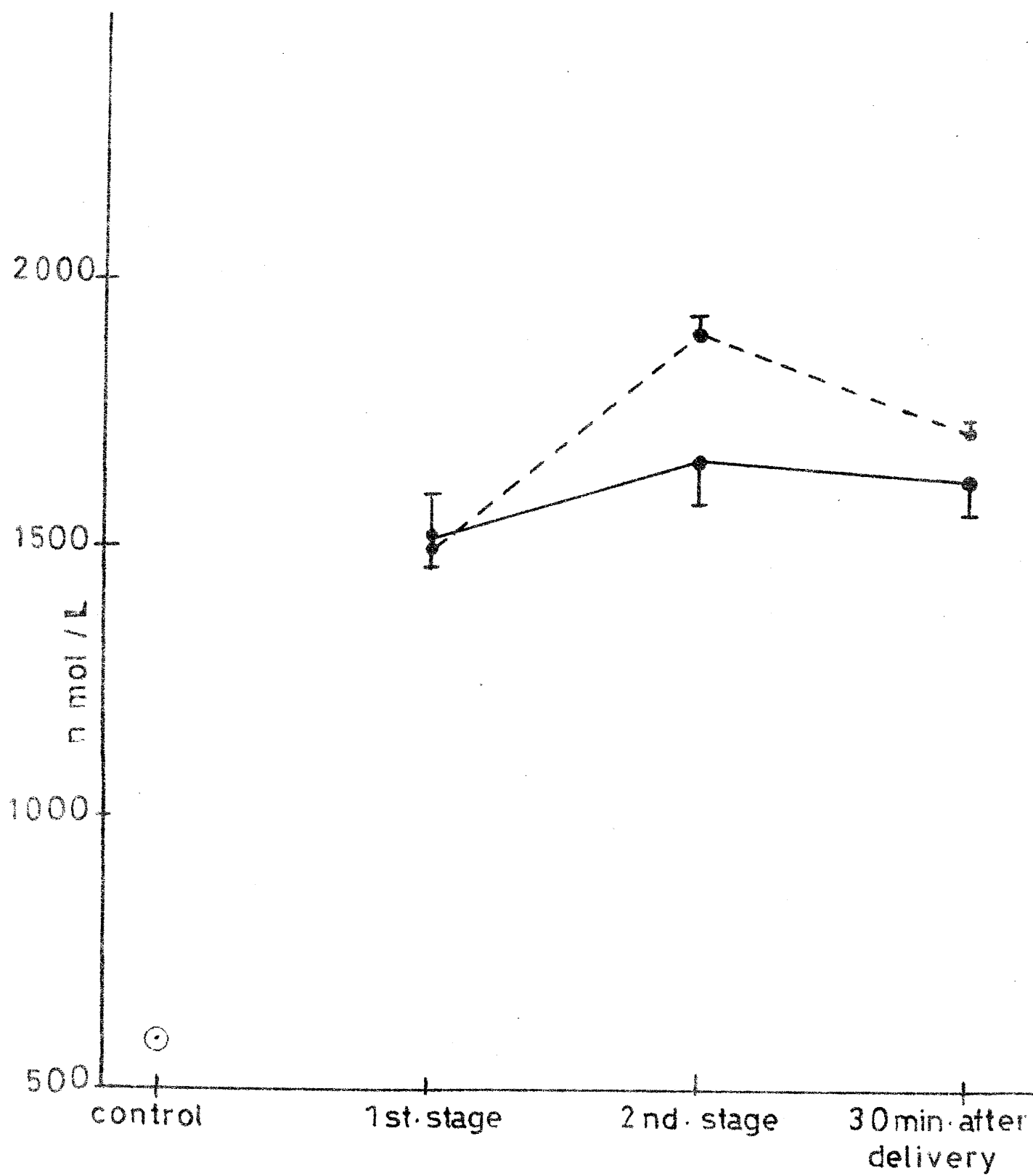


Fig. 5.7 Plasma Cortisol (n mol/L), in 22
spontaneous labour ————, in
6 induced labour - - - - - and
in 12 pregnant women before
labour ⊙.



DISCUSSION

The data presented show clearly that, during labour stimulated with oxytocin, the subjects were able to raise their plasma levels of FFA at a similar rate to those of spontaneous labour. This occurred despite the presence of hyperglycemia, thus indicating that, the rate of fat mobilization is similar whether labour is spontaneous or oxytocin induced as previously demonstrated by Kashyap et al (1976), so long as the oxytocin is used in physiological amount. The marked fall in plasma FFA concentrations noted by Fairweather (1965) in labour following oxytocin and glucose infusion, however, is not seen in this study, though there appears to be a tendency toward smaller degree of ketosis. These findings suggest that, during labour although the rate of fat mobilization is not appreciably affected by oxytocin and glucose administration, the rate of fat oxidation appears to increase.

The rise in blood glucose concentrations when the subjects were in labour was compatible with the observation of (Kashyap et al, 1976), since all the subjects did mobilize fat, it is possible that there was a decrease in the peripheral uptake of glucose and its subsequent oxidation (Butterfield et al, 1965). This could have been exaggerated by both increased fat and ketone body utilization and also glucose administration particularly in the subjects undergoing induced labour.

The rise of blood lactate and pyruvate in response to labour was greater with oxytocin induced than with spontaneous labour. This is unlikely to be related only to the concentration of glycogen in the working muscle involved in response to labour, but it is possible that increased oxidation of ketone bodies and FFA may facilitate anaerobic glycolysis and lactate production by decreasing the intracellular oxidation of glucose (Katz Landau and Bartsch, 1966). It is well documented that lactate inhibit lipolysis in human (Boyed, Giamber Mager and lebovitz, 1974). The present work indicate that lactic acidemia during labour fails to inhibit maternal fat mobilization during labour. However high lactic acid concentrations and low FFA levels were observed in the foetal blood at birth by other workers.

Lactic acid and glucose pass the placenta readily, it is likely therefore, that the marked maternal lactate production allows some transfer across the placenta so that this transfer limit foetal fat mobilization and spare glucose as a metabolic fuel for the foetus during labour.

SUMMARY AND CONCLUSION

In the introduction to this thesis I explained that the purpose of these investigation was to establish the usual response of blood metabolites and hormones to labour. The second purpose was to compare the responses in altered nutritional state and following the administration of oxytocin in glucose solution.

The subjects were admitted to the labour ward after selection by the obstetrician in charge. None of them suffered from obstetrical or medical complication, they were allowed fluid diet during the first stage of labour. Venous blood was taken at the first stage when labour was well established, during the second stage of labour and 30 minutes after delivery and analysed for fat and carbohydrate metabolites.

The findings reported in chapter 4 demonstrated that the size and the direction of blood metabolite and hormone changes during labour vary with obesity. Compared to normal weight subjects, obese individuals mobilize fat in excess for there need as indicated by the amount of glycerol and FFA released. In addition they have higher concentrations of blood lactate, pyruvate and ketone bodies during labour. This would suggest that the FFA mobilized during labour is apparently more efficiently oxidised in normal weight subjects. In obese subjects, however, in complete oxidation of fat causes a considerable rise in

blood ketone bodies. The obese subjects also showed a higher blood glucose levels throughout and this may be due to the utilization of FFA and ketone bodies as adaptation by the maternal body to spare glucose for the requirement of the nervous system.

Experience gained from the previous studies on the utilization of metabolic fuel in response to labour started spontaneously have made it to compare energy metabolism in women following the administration of oxytocin in glucose solution as a labour inducer.

In comparison with spontaneous labour, during oxytocin induced labour, mobilization of fat and ketosis occurred in spite of the availability of glucose.

These metabolic changes clearly demonstrate that during labour whether it is spontaneous or induced with oxytocin, maternal energy is provided apparently more from the oxidation of fat and fat derived substances. In addition to these adaptation, labour also increases the mechanism for lactic acid production. Lactic acid a potent antilipolytic agent is known to cross the placenta readily and may consequently act to limit fat mobilization and spare liver glycogen in the foetus through gluconeogenic processes.

From these observation of the metabolic responses to labour, I conclude that, the production of ketone bodies and lactate are of biological necessity to spare glucose, nevertheless their presence as a metabolic acids may in danger the out come of pregnancy, clinical measures to control acidosis may be required.

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في مقدمة هذه الاطروحة اوضحت بان الهدف من اجراء هذه البحوث هو تحمين التغيرات الحيوية الحاصلة في الايض الغذائي والهرمونات في الدم اثناء عملية الولادة في الانسان اولا ، ومن ثم دراسة مقارنة حول تأثير البدانة على هذه التغيرات الحيوية وكذلك اجراء دراسة مقارنة بين هذه التغيرات في ولادات طبيعية واخرى محدثة بواسطة اعطاء مادة (Oxytocin) في محلول سكر الكلوكوز بالوريد كمحفز للولادة .

ان النساء اللواتي اجري عليهن الاختبار ادخلن الى صالة الولادة بعد اختيار الطبيب المولد لهن وجميعهن كن يتمتعن بصحة جيدة ولا يمانين من اى مضاعفات طبية اثناء الحمل ، هذا وقد سمح لهن بم تناول السوائل في المرحلة الاولى من عملية الولادة .

اما نماذج الدم فقد اخذت من الوريد في ثلاث مراحل الاولى وفي المرحلة الثانية من عملية الولادة ثم بعد الولادة بنصف ساعة . وقد اجريت الفحوصات اللازمة لمعرفة تراكيز المواد الكربوهيدراتية والدهنية في الدم في كل هذه المراحل ، اضافة الى تركيز هرمون الكورتيزول .

ان النتائج الواردة في الفصل الرابع تظهر لنا مدى تأثير البدانة على حجم واتجاه التغيرات الحيوية في الايض الغذائي اثناء عملية الولادة ، حيث ان تحرك الدهون في النساء البدينات هو أكثر مما عليه في النساء ذوات الاوزان المعتدلة كما هو ظاهر من كمية الكليسورل والحوامض الشحمية المتحررة في الدم . بالاضافة الى ذلك ، فان كمية حامض اللبنيك والبيروفيت والاجسام الكيتونية في الدم هي ايضا اعلى في النساء البدينات اثناء الولادة . ان هذه النتائج توحي بان اكسدة الحوامض الشحمية كليا في نساء ذوات اوزان معتدلة هي اعلى نسبة مما هي عليه في ذوات الاوزان العالية حيث ان معظم الحوامض الشحمية لا تتأكسد تماما مما سبب زيادة في انتاج الاجسام الكيتونية ، كذلك فان كمية سكر الكلوكوز في الدم هي ايضا

اعلى نسبة في النساء البدينات وقد يعود ذلك الى استخدام الحوامض الشحمية والاجسام الكيتونية كوقود احتياطي للكلوكوز لسد حاجة الجهاز العصبي اثناء عملية الولادة •

في هذا البحث اجريت ايضا مقارنة بين الوقود الايضي المستخدم في ولادات طبيعية وولادات محدثة وقد تبين ان تراكيز الاجسام الكيتونية قد ازدادت ايضا في الولادات المحدثه بالرغم من توفر الكلوكوز وهذه الزيادة توضح بان عملية الولادة سواء كانت طبيعية او محدثة فان الطاقة المستخدمة تنتج من اكسدة المواد الدهنية •

بالاضافة الى ما تقدم فان عملية الولادة تزيد ايضا كمية حامض اللبنيك في الدم •

من المعلوم ان هذا الحامض يحد من تحرك الحوامض الشحمية في الانسجة الدهنية ويمرر خلال المشيمة الى الجنين ويمنع تحرك الدهون وقد يستخدم كطاقة احتياطية لمادة الكلايكوجين في الجنين اثناء تكوين السكر •

من ملاحظاتي حول تأثير الولادة على الايض الخدائي فانني استنتج ان الاجسام الكيتونية وحامض اللبنيك يستخدمان كوقود احتياطي هام للسكر اثناء عملية الولادة بالرغم من ان وجود هذه الحوامض في الدم قد يسبب اخطارا على صحة المرأة والجنين وان الحاجة لاجراء فحوصات طبية للسيطرة على نسبة هذه الحوامض في الجسم قد تكون ضرورية احيانا •