The data derived from this study and information on the structure of the female population of England and Wales derived from the Registrar General's report make it possible to estimate the mortality from myocardial infarction in women who use oral contraceptives and in those who do not. In the 30-39-year age group the yearly death rate in women not using these preparations is estimated to be 1·9 per 100 000 compared with 5·4 per 100 000 in women who are using them. In the 40-44-year age group the yearly death rates are 11·7 and 54·7 per 100 000 respectively.* It seems, then, that the risk of death from myocardial infarction was increased about 2·8 times in current users of oral contraceptives aged 30-39 years and about 4·7 times in women aged 40-44 years.

In absolute terms the attributable mortality was considerably lower in women aged 30-39 years than in those aged 40-44 years, there being an excess of 3·5 deaths per 100 000 users yearly in the former group and 43 per 100 000 users yearly in the latter group. These estimates of risk are similar to the increased risk of non-fatal infarction estimated by Mann *et al.*[11] but still need to be interpreted with caution, as a number of assumptions have necessarily had to be made in their calculation and the margin of error is likely to be fairly wide. We do, nevertheless, consider them to be helpful in providing a crude estimate of risk of death from myocardial infarction in women currently using oral contraceptives.

*These data are too few to justify making estimates for women aged 45-49 years, in whom the yearly mortality rate in 1973 (in users and non-users combined) was 29·4 per 100 000.

We are grateful to the medical officers on the committee's staff who carried out the interviews, to the many doctors who gave their time to provide us with information, and to Sir Richard Doll and Professor M. P. Vessey for advice and encouragement. Dr. A. M. Adelstein and Mr. J. G. Gerrard, of the Office of Population Censuses and Surveys, kindly arranged for us to receive the transcripts of death certificates. Miss A. Renauld, Mrs. M. Spellman, and Mrs. G. Mead provided invaluable secretarial help, and Mrs. M. Thorogood and Mr. R. Golding and his staff, of the Oxford Regional Health Authority, helped with the analysis of the results. J.M. was supported by an I.C.I. Fellowship and by the Cecil John Adams Memorial Fellowship during the period of this study. We are grateful to Sir Eric Scowen and the Committee on Safety of Medicines for permission to report these data.

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Maintenance of Labour

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British Medical Journal, 1975, 2, 248-250

Summary

In 160 women large but variable amounts of intravenous oxytocin were needed to induce labour within a reasonable time interval to 5 cm cervical dilatation. Thereafter 7 mU of oxytocin/min would maintain progress. Since larger maintenance doses may cause obstetric problems it is recommended that a maintenance regimen should be used once labour has progressed to this stage.

Introduction

Induction-delivery intervals much over 12 hours are no longer acceptable. Small quantities of oxytocin (Syntocinon) infused intravenously for prolonged periods induce labour in many women who are near term. To ensure induction in all patients within a reasonable time, however, methods such as oxytocin titration[1] and an increasing rate of infusion have been developed. Little attention has been paid to the maintenance of labour after such regimen. We have studied the modern process of labour stimulation to see whether a stage is reached beyond which oxytocin requirements are greatly reduced.

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Patients and Methods

Labour was induced in 83 multiparous and 77 primiparous women between 266 and 294 days of gestation. The indications for induction are shown in table I. All the fetuses presented cephalically. Except for women excluded because of possible cephalopelvic disproportion consecutive patients were treated.

TABLE I—*Indications for Induction of Labour*

	No. of Primiparae	No. of Multiparae
Hypertension (including pre-eclamptic toxaemia)	30	31
Prolonged pregnancy (≥ 290 days)	45	45
Elderly primigravida (> 35 years)	1	
Latent diabetes		2
Poor obstetric history		2
Suspected fetal dysmaturity		3
Threatened abortion in early pregnancy	1	
Total	77	83

Intravenous oxytocin infusion was started immediately after low amniotomy in all patients. At the time of amniotomy the Bishop score was estimated according to the criteria in table II. The dose regimen used for increasing oxytocin is shown in table III. After starting

induction a pelvic examination was performed on each patient (*a*) at the end of the latent interval—that is, at about the time regular uterine contractions of at least 30 seconds of duration were occurring at intervals of three minutes—or (*b*) thereafter, when it was estimated clinically that the cervix might have achieved a predetermined dilatation. On completion of the latent interval and at various stages of cervical dilatation thereafter the infusion was reduced to 7 mU/min in each patient. If three to four hours later the patient remained undelivered or delivery was not imminent a second pelvic examination was performed.

All estimates of cervical dilatation were plotted on established partograms[2] and the rate of progress was compared with the slope of the standard partogram and classified as either slow or satisfactory. When progress was satisfactory with an infusion rate of 7 mU/min treatment was not altered. If labour was slow or had stopped the rate was increased until effective contractions became established (table III). This rate was maintained until delivery.

TABLE II—*Bishop Score*

	Length of Cervix	Dilatation of Cervix	Consistency of Cervix	Position of Cervix	Station of Presenting Fetal Part
0	3 cm	Closed	Hard	Posterior	> 3 cm above ischial spines
1	2 cm	1-2 cm	Intermediate	Intermediate	2-3 cm above ischial spines
2	1 cm	3-4 cm	Soft	Anterior	< 2 cm above ischial spines
3	Fully effaced	5 cm			Below ischial spines

TABLE III—*Method of Oxytocin Increase Used for Induction after Low Amniotomy*

Time after Low Amniotomy (Min)	Intravenous Oxytocin Infusion (mU/Min)	Equivalent Drops/Min (10 Units Oxytocin/l)
0	2·8	4
15	4·2	6
30	5·6	8
45	7·0	10
60	10·5	15
75	14·0	20
90	17·5	25
105	21·0	30
120	28·0	40
135 and over	35·0	50

Results

INDUCTION OF LABOUR

In both the primigravid and multiparous women the mean interval from the start of induction to clinical evidence of established labour diminished as the Bishop score increased (table IV). With each Bishop score the latent interval varied. Nevertheless, cumulative frequency tables showed that in all primigravidae labour was established within four hours when the score was 9 or more at the start, within six hours when it was 7-8 at the start, and within eight hours when it was 6 or less at the start. In multiparous women labour was established within four hours when the score was 9 or more at the beginning of the regimen. When the score was either 1-2 or 5-6 at the start labour was always established within six hours. With scores of 7-8 and 3-4 labour was not established in all multiparae until after eight hours.

The mean total dose of oxytocin infused during the latent interval varied from 1·24 ± 2·46 to 7·64 ± 5·46 U in primigravid patients and 1·24 ± 1·91 to 4·28 ± 3·99 U in multiparous women.

MAINTENANCE OF LABOUR

Labour was maintained satisfactorily in only three out of 22 women (13·6%) in whom the infusion of oxytocin was reduced to 7 mU/min when dilatation of the cervix was less than 2 cm. In contrast, when dilatation had reached 5 cm or more when the infusion was reduced progress continued satisfactorily in all women (table V). There was no significant difference between the primigravid and multiparous women (tables VI and VII).

TABLE IV—*Relationship of Bishop Score to Mean Latent Interval after Amniotomy*

Bishop Score	Mean Interval ± S.D. (h)	
	Primigravidae	Multiparae
1-2	5·1 ± 2·6	3·5 ± 1·9
3-4	3·3 ± 1·1	3·0 ± 1·5
5-6	2·7 ± 1·7	2·6 ± 1·2
7-8	2·7 ± 0·8	2·4 ± 1·3
9-10	2·5 ± 0·6	2·4 ± 0·9
11-12	2·0 ± 0·9	2·0 ± 0·7

TABLE V—*Summary of Results*

Cervical Dilatation after Standard Induction Regimen (cm)	No. of Patients	On Reduced Oxytocin Regimen (7 mU/Min)		
		Patients Delivered	Labour Delayed	Labour Stopped
1-2	22	3	6	13
3-4	60	46	8	6
5-6	48	48		
7-8	30	30		
Total	160	127	14	19

TABLE VI—*Summary of Results in Primigravidae*

Cervical Dilatation (cm) after Standard Induction Regimen	No. of Patients	On Reduced Oxytocin Regimen (7 mU/Min)		
		Patients Delivered	Labour Delayed	Labour Stopped
1-2	14	3	4	7
3-4	33	25	5	3
5-6	14	14		
7-8	16	16		
Total	77	58	9	10

TABLE VII—*Summary of Results in Multiparae*

Cervical Dilatation (cm) after Standard Induction Regimen	No. of Patients	On Reduced Oxytocin Regimen (7 mU/Min)		
		Patients Delivered	Labour Delayed	Labour Stopped
1-2	8		2	6
3-4	27	21	3	3
5-6	34	34		
7-8	14	14		
Total	83	69	5	9

Discussion

All these women showed a variable response to a standard induction regimen. Our results show that to obtain a reasonably short induction-delivery interval, quite large but variable quantities of oxytocin are often required to induce labour, but smaller amounts will maintain progress once labour has become established. Patients who achieved a dilatation of 5 cm or more continued in satisfactory labour when the infusion rate of intravenous oxytocin was reduced to 7 mU/min. Their partograms also indicated that while on this regimen the progress of labour did not exceed the rate for normal spontaneous labour.

In primigravid women a Bishop score of 9 or more correlated with a fairly short latent interval after induction. In multiparae, with all scores the mean latent interval was shorter than in primigravidae. Nevertheless, labour was induced only after eight hours in a few multiparae whose scores totalled 3-4 or even 7-8. This observation agrees with our general experience that it may be unexpectedly difficult to induce labour in some multiparous patients.

At a time when no more than a maintenance infusion of oxytocin is required overstimulation of uterine activity might be expected to cause numerous difficulties, including uterine

hypertonus, intrapartum fetal anoxia, rapid labour, and deep transverse arrest of the fetal head. We therefore made a limited comparison between the methods of delivery used in this study and for 945 women of similar gestation and in whom there was no clinical suspicion of cephalopelvic disproportion and who were delivered in the same hospital during 1973. In both groups all labours were induced by an identical technique, except that in 1973 once labour became established the oxytocin infusion rate was not reduced to 7 mU/min but was maintained at a greater though constant rate.

The incidence of normal delivery was similar in both groups. In the present study no ventouse extractions were necessary and no caesarean sections were performed. In 1973 3% of the patients were delivered by these methods. Fetal distress was never the indication for operative intervention in patients receiving only 7mU oxytocin/min to maintain labour. In 1973 fetal distress, confirmed by blood pH estimation, was the chief indication for operative delivery in 32% of the group.

Whereas variable amounts of oxytocin are required to induce labour to the stage of 5 cm dilatation of the cervix within a reasonably short time, our results show that no more than 7 mU/min is necessary to maintain labour satisfactorily thereafter. Larger doses at this time may be attended by obstetric problems. We therefore recommend the adoption of a maintenance regimen whenever established labour has been induced.

We are grateful to the nursing staff of the labour ward at Mill Road Maternity Hospital for their help, and to our colleagues Mr. R. D. Atlay and Mr. D. Prysor-Jones for access to patients under their care.

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Volunteer and Clinical Studies with Carfecillin: A New Orally Administered Ester of Carbenicillin

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British Medical Journal, 1975, 2, 250-252

Summary

Blood and urine levels of carbenicillin were measured in 10 healthy volunteers and four patients with renal failure after single and multiple oral doses of carfecillin. Urinary levels after 1000-mg doses in healthy subjects were considered sufficient for treatment of *Pseudomonas aeruginosa* urinary infections, but the serum levels were too low for chemotherapy of systemic infections with this organism even in severe renal failure.

Urinary infections were treated in 35 inpatients with a seven-day course of carfecillin. The infection was eradicated in 21 cases (60%). In 12 cases the pathogen was *Ps. aeruginosa*, which was eradicated from eight patients (67%). Many patients had severe urinary tract disease. Side effects were virtually absent.

Introduction

Carfecillin (Uticillin) is the phenyl ester of carbenicillin substituted in the α-carboxyl position on the active side chain, which greatly increases the oral absorption of the drug. Esterification is a well-known method of increasing the absorption of antibiotics from the gastrointestinal tract—for example, the esters of erythromycin. Once absorbed, carfecillin is rapidly hydrolysed to carbenicillin and phenol,[1] the phenol moiety being quickly detoxicated by conjugation as glucuronide and sulphate and excreted in the urine. Excretion of the antibiotic is predominantly renal and high levels of carbenicillin appear in the urine though the relatively short serum half life, even in severe renal failure,[2] would suggest either a natural loss of antipseudomonal activity in vivo or else an extrarenal pathway of excretion.

This study was designed to investigate the human pharmacology and toxicology of carfecillin and assess the drug's value in treating urinary infections in hospital inpatients, particularly those in whom *Pseudomonas aeruginosa* was the causative pathogen.

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Patients and Methods

VOLUNTEER STUDY

Carfecillin 500 mg or 1000 mg by mouth (equivalent to 397 mg and 794 mg of carbenicillin free acid respectively) was given to 10 healthy volunteers two hours after a light breakfast of beverage and toast. Carbenicillin levels were assayed in serial blood samples over eight hours during which about 125 ml of water was allowed every half hour. Urinary recovery of carbenicillin was measured over three consecutive four-hour periods from the beginning of the study. All serum and urine carbenicillin concentrations were assayed by a well-plate microbiological diffusion assay method using *Ps. aeruginosa* (NCTC 10490) as test organism. Serum samples were also investigated for the presence of free phenol by a standard gas-liquid chromatographic method, using an ether/acid extraction process which could detect less than 0·5 mg/l free phenol.

Four of the volunteers subsequently took either 500 mg or 1000 mg of carfecillin every eight hours over four days while receiving their normal diet. Serial carbenicillin levels were determined as before on days two and four, and all urine was collected for assay throughout the period.

Four patients with renal failure (creatinine clearance $\leqslant$ 2·2 ml/min) who had given informed consent took either two or three doses of carfecillin 1000 mg by mouth at four-hourly intervals. Serum carbenicillin levels were assayed throughout the period. Two of the patients were anuric, so urinary carbenicillin levels were measured only in two.

THERAPEUTIC TRIAL

A therapeutic trial of carfecillin in 35 inpatients with urinary infections was then undertaken. Doses of 1000 mg were given by mouth every eight hours for seven days. Serum levels of carbenicillin were measured in 18 patients one and two hours after the initial dose, and the urinary recovery of carbenicillin was determined in all patients