appreciable follicular development. It may be that the margin of contraceptive effectiveness of this lower-dose formulation is less than that of earlier preparations. There were no untoward clinical findings during the two high oestrogen output cycles. It would be very difficult to determine clinically the incidence of contraceptive cycles in which the output of oestrogen was raised. Nevertheless, the fact that such high levels of endogenous oestrogen output does occur during the administration of a lower-oestrogen-containing oral contraceptive raises the question whether it is indeed the dose of oestrogen per se which bears a relation to the incidence of thromboembolism. Clearly, the combination of a particular progestogen with the oestrogen has some, as yet undetermined, influence on this, as the lower incidence of thromboembolism with the combined pill comprising norethynodrel and mestranol would suggest (Inman *et al.*, 1970).

The recommendations of the Committee on Safety of Medicines were related to a fixed dose of both types of oestrogen currently found in combined oral contraceptive formulations, even though ethinyl oestradiol has a greater oestrogenic action in humans than that of mestranol (Delforge and Ferin, 1970). There are other differences in the effect of these two oestrogens on carbohydrate metabolism (Di Paola *et al.*, 1968), liver function (Eisalo *et al.*, 1968), and also vitamin B₆ metabolism (Luhby *et al.*, 1971). Clearly, further studies of a similar nature to this with a combined contraceptive formulation comprising ethinyl oestradiol instead of mestranol at a dose of 50 µg or even less and 1 mg of norethisterone will provide further interesting data, and these studies are under way.

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Closing Volume and Pregnancy

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Summary

Measurements of closing volume have been made in 20 women between the 36th and 40th weeks of pregnancy. The patients were studied in the erect and supine positions and the point of airway closure was related to functional residual capacity. The results show that airway closure occurred during tidal ventilation in 10 patients in the erect position and in six patients in the supine position. These results may explain the variation found in maternal arterial oxygen tension during pregnancy.

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Introduction

The changes in maternal ventilation which occur during pregnancy are now well established. Increases in minute volume and oxygen consumption are seen from early pregnancy (Magnus-Levy, 1904). The increase in minute volume, which seems to be an accentuation of the normal changes occurring during the menstrual cycle, may result in a progressive fall in the arterial Pco₂ during pregnancy (Prowse and Gaensler, 1965). These changes are probably due to hormonal secretion as they occur before the increased demand of the fetus appears.

Changes in lung volumes occur only during the last trimester. Though there is little change in vital capacity there are considerable falls in expiratory reserve volume and residual volume (RV) and consequently in functional residual capacity (FRC) (Cugell *et al.*, 1953). These changes are due to the mechanical presence of an intra-abdominal tumour tending to force the diaphragm into the chest.

Reported measurements of maternal arterial oxygen tension show wide variation. Despite the hypocapnia they tend to be lower than in non-pregnant women of the same age (Stenger *et al.*, 1964). The cause of this fall in arterial oxygenation is unknown but has been attributed to cardiovascular and respiratory disturbances (Ang *et al.*, 1969). A fall in FRC in other situations—for example, after surgery (Craig *et al.*, 1971; Alexander *et al.*, 1972)—results in impaired distribution of pulmonary ventilation. This impaired distribution may be detected by measurement of the "closing volume" which is the lung volume during expiration at which airways begin to close

in the dependent zones of the lungs (Leblanc *et al.*, 1970). If abnormalities in the distribution of ventilation occur during tidal ventilation the resulting pulmonary venous admixture will result in a fall in arterial oxygen tension.

The present study was designed to determine whether there was any abnormality in the distribution of pulmonary ventilation during the last month of pregnancy. An attempt was also made to determine whether such an abnormality, if it was found to occur, could result in impaired arterial oxygenation during tidal ventilation.

Materials and Methods

Twenty women between the 36th and 40th weeks of pregnancy were studied (table I). Their ages ranged from 19 to 39 years and their weight from 51 to 86 kg. They were admitted to hospital for a variety of conditions but none had any respiratory symptoms. Each patient was studied while sitting erect on a cardiac bed with her head supported, her back 80° from horizontal, thighs 90° to her trunk, and knees flexed to 90°, and also while lying supine. The supine position caused no discomfort to any patient.

TABLE I—Details of Patients

Case No.	Age	Weight (kg)	Duration of Pregnancy (Weeks)	Reason for Admission
1	33	74	37	Hypertension
2	38	73	38	Unstable lie
3	23	60	39	Hypertension, static weight and girth
4	35	65	40	Hypertension
5	26	86	36	Hypertension
6	23	84	38	Porphyria antepartum haemorrhage
7	18	58	36	Breech
8	33	70	37	Twins
9	34	51	36	Premature labour, psychosis
10	29	71	37	Static weight and girth
11	39	75	39	Static weight and girth, elderly primigravida
12	25	71	39	Hypertension
13	26	59	40	Static weight and girth
14	22	69	38	Previous miscarriage
15	40	56	40	Hypertension
16	23	73	40	Unstable lie, static weight and girth
17	34	84	39	Hypertension
18	22	73	39	Anaemia
19	25	69	36	Twins
20	19	53	36	Hypertension

Closing volume was measured according to the method of Anthonisen *et al.* (1969). The subject, breathing room air, exhaled to RV and then slowly inspired 100% oxygen to total lung capacity (TLC). After a pause of 2 or 3 seconds she re-expired slowly to RV into a spirometer. The rates of inspiration and expiration were always less than 0.5 l./sec. The spirogram and the expired nitrogen concentration, measured at the mouth,

FIG. 1—Typical closing volume trace. VC=Vital capacity. CV=Closing volume. CP=Point of airway closure.

were recorded simultaneously on an ultraviolet recorder. The nitrogen concentration was measured with a Nitralyser (Exal, Ltd.) with a measured 95% response time of 160 msec.

The expired nitrogen concentration trace had the typical four components (labelled from 1 to 4, Dolfuss *et al.*, 1967) as seen in fig. 1. The "knee" or steep increase in concentration from the alveolar plateau was clearly seen. The volume from this point to RV will be called the "closing volume." Five measurements were made in both the sitting and supine positions.

Measurements of tidal volume (VT), vital capacity (VC), and expiratory reserve volume were made by conventional closed-circuit spirometry (C. F. Palmer, High Wycombe). For each patient the difference between expiratory reserve volume and closing volume (ERV-CV) after correction for nitrogen meter delay was calculated. A negative value signified that airway closure had occurred during tidal ventilation.

Results

The mean of all measurements of closing volume, even when no closing occurred, VC, and the mean of three measurements of expiratory reserve volume in both sitting and supine positions are given in table II.

The mean values for the lung volumes in the sitting position of all the patients are shown in fig. 2. RV has been calculated assuming $RV=20\%$ TLC. In addition, the mean value for the

TABLE II—Mean Values (ml) for Closing Volume (CV), Vital Capacity (VC), and Expiratory Reserve Volume (ERV)

Case No.	Sitting Erect				Supine			
	CV	VC	ERV	ERV-CV	CV	VC	ERV	ERV-CV
1	1,200	3,425	350	-850	318	3,300	295	-23
2	390	2,598	587	+197	183	2,460	587	+404
3	749	2,178	408	-341	97	1,946	394	+297
4	443	3,348	666	+223	0	3,207	610	+610
5	394	3,597	370	-24	287	3,370	490	+203
6	650	3,057	755	+105	145	2,760	410	+265
7	134	1,890	180	+46	93	1,582	170	+77
8	243	3,116	677	+434	414	2,860	268	-146
9	188	3,010	686	+498	262	2,920	426	+164
10	382	3,366	930	+548	223	3,378	460	+237
11	710	3,154	385	-335	542	2,708	275	-267
12	310	2,266	300	-10	198	2,122	280	+82
13	176	3,013	515	+339	123	2,398	520	+397
14	22	2,625	330	+308	65	2,230	270	+205
15	621	2,806	603	+18	196	2,310	321	+125
16	717	3,330	465	-252	465	3,066	303	-162
17	263	2,545	253	-10	220	1,725	233	+13
18	804	3,777	590	-214	700	3,278	272	-428
19	602	2,534	360	-242	411	2,516	168	-243
20	192	2,296	475	+283	168	2,231	242	+74

FIG. 2—Mean values of CV in individual patients in erect position related to functional residual capacity (FRC). Mean values for erect lung volumes in all patients shown left. IRV=Inspiratory reserve volume. VT=Tidal volume. ERV=Expiratory reserve volume. RV=Calculated residual volume.

closing volume in each patient is plotted in relation to FRC. Thus, in the sitting position, closure of dependent airways occurred during tidal ventilation in half of the women.

The same measurements in the supine position are shown in fig. 3. Airway closure in this position occurred in six of the 20 women during tidal ventilation.

FIG. 3—Mean values of CV in individual patients in supine position related to FRC. Mean values for supine lung volumes shown left.

Discussion

These findings show that in the last month of pregnancy closure of dependent airways occurred above FRC in 10 out of 20 patients in the sitting position and in six out of 20 in the supine position. Though these women were admitted for a variety of conditions there is no reason to suggest that the cause of their admission was related to these changes. Non-pregnant women of a similar age have a closing volume well below FRC (Collins *et al.*, 1973). Such abnormality, by producing abnormal distribution of pulmonary ventilation with its resulting ventilation:perfusion inequality and pulmonary venous admixture, would lead to impaired arterial oxygenation if there was no change in the distribution of pulmonary perfusion. Though closing occurred earlier in all patients in both positions than in the case of normal individuals, there was a wide range of closing volumes in this study. This might explain a similar scatter in arterial oxygen tensions previously described during late pregnancy (Stenger *et al.*, 1964). More women had airway closure above FRC in the sitting than in the supine position but the difference is probably due to the wide scatter of results in a relatively small number of patients. Studies of arterial oxygenation during pregnancy show a fall in arterial oxygen tension

when the patient is moved from the sitting to the supine position (Ang *et al.*, 1969).

The measurements of lung volumes by spirometry are in agreement with other authors (Thompson and Cohen, 1938; Cugell *et al.*, 1953). Vital capacity fell slightly but there was a noticeable decrease in expiratory reserve volume compared with normal values (Comroe *et al.*, 1965). If it is assumed that $RV = 20\%$ TLC then this suggests a considerable fall in FRC. It has been shown that the point of airway closure can be predicted from measurements of TLC and the age of the patient (Collins *et al.*, 1973). At age 30 in non-smoking subjects closure occurs at 32% (± 5) TLC in the sitting erect position. The normal TLC of a 30-year-old woman is 4,200 ml (Comroe *et al.*, 1965). Thus airway closure will occur at a lung volume between 1,440 and 1,580 ml. In the present study, with an assumed value for RV of 20% TLC, the mean point of closure occurred at a lung volume of 1,175 ml (mean value for closing volume + assumed RV). Thus it seems that the findings would support the hypothesis that the apparent increase in closing volume merely represents a fall in FRC—airway closure occurring at the same lung volume. There is no reason to postulate changes in distal airways. Indeed, previous studies have shown that there is a fall in (proximal) airway resistance presumed to be due to female hormones and relaxin.

Thus these findings are in agreement with previous studies which showed that in situations where there is a fall in FRC airway closure may occur during tidal ventilation and result in impaired arterial oxygenation.

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