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Research Article

Small for Gestational Age Fetus, Maternal Haemoglobin and Cardiac Output at Mid Pregnancy

S Chhabra[1]*, S Chopra[2] and M Rewatkar[3]

[1]Director Professor, Obstetrics Gynaecology, Mahatma Gandhi Institute of Medical Sciences, Sevagram - Wardha, Maharashtra, India

[2]Ex Post Graduate Student, Obstetrics Gynaecology, Mahatma Gandhi Institute of Medical Sciences, Sevagram - Wardha, Maharashtra, India

[3]Ex. Assistant Professor, Obstetrics Gynaecology, Mahatma Gandhi Institute of Medical Sciences, Sevagram - Wardha, Maharashtra, India

***Corresponding Author**: S Chhabra, Director Professor, Obstetrics Gynaecology, Mahatma Gandhi Institute of Medical Sciences, Sevagram - Wardha, Maharashtra, India.

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Abstract

Background: Physiologic changes in mother's body, growth and development of fetus are interlinked. By 8 weeks of gestation there are dramatic alterations in cardiovascular physiology. Cardiac output increases by 30 - 50% during pregnancy, 50% of this increase occurs by 8 weeks gestation. Initial increase is a result of reduced systemic vascular resistance, increase in stroke volume (SV). If this increase is impeded or abolished by pathological factors, placental circulation is affected, which affects foetal growth and development.

Objective: Objective was to know relationship between small for gestational age babies diagnosed at mid pregnancy with maternal haemoglobin and cardiac output.

Material and Methods: Prospective study was conducted in 500 women with clinical, sonographic evidence of small for gestational age fetus at mid pregnancy, to know relationship of SGA baby with maternal haemoglobin and cardiac output at mid pregnancy and beyond. Controls had similar demography but no clinical, sonographic evidence of SGA baby. Study, controls were divided into, with and without anaemia (mild, moderate and severe anaemia). CO, Haemoglobin were measured at 20 - 24 weeks, 28 - 32 weeks, 37 - 42 weeks. Study was about relationship between SGA, anaemia and CO at mid gestation and beyond and not effects of therapy of anaemia. Whatever was happening was recorded on predeveloped tool.

Results: Among study 79.2%, amongst controls 63.4% were anaemic. Number of anaemic mothers didn't change with advancing gestation, though degree of anaemia changed with gestation. Mean CO in SGA cases with mild anaemia was higher than non - anaemic mothers with SGA baby at all gestations, difference insignificant. Mean CO in cases with SGA baby in women with moderate, severe anaemia were significantly higher than non anaemic cases with SGA baby. CO was higher in controls than study cases with similar severity of anaemia. Anaemia did cause increase in CO in mothers even with SGA babies, but CO was significantly less than controls having similar severity of anaemia but no SGA baby. More research is needed.

Keywords: *Mid pregnancy; Small Gestational Age Fetus; Cardiac output; Anaemia*

Background

Physiologic changes in the mother's body and the growth and development of the fetus are interlinked. By 8 weeks of gestation there are dramatic alterations in cardiovascular physiology [1]. Cardiac output increases by 30 - 50% during pregnancy and 50% of this increase occurs by 8 weeks gestation [2 - 5]. The initial increase is the result of reduced systemic vascular resistance and increase in stroke volume (SV) [6,7]. If this increase is impeded or abolished by pathological factors, placental circulation is affected, which affects the foetal growth and development [8 - 10]. However, foetus also might affect this change. Pregnancies complicated by small babies appear to lack the stimulus to induce the hemodynamic changes present in a normal pregnancy [6,11,12]. Further heart responds to anaemia by increase in CO to maintain adequate oxygen delivery to body systems. However, anemia by causing hypoxia and iron deficiency, by increasing serum norepinephrine also induce maternal and fetal stress, which stimulate the synthesis of corticotropin - releasing hormone (CRH), which increases fetal cortisol production, which is likely to inhibit growth of the fetus. Foetus gets affected by maternal haemoglobin levels below 8.0 g/dl [13 - 15]. Anemia leads to growth reduction. Maternal CO is less in women who have small for gestational age (SGA) babies. But the physiological response to anemia is a compensatory increase in CO. These contradictions raise an important question about happenings in pregnancies with obvious SGA and anaemia.

Objective

Objective was to know relationship between SGA babies diagnosed at mid pregnancy with maternal haemoglobin and cardiac output.

Material and Methods

Prospective study was carried out in Obstetrics Gynaecology with the help of department of Physiology. Approval of institute's ethics committee was taken as is the practice for all such studies. Informed consent was taken from each subject. The study subjects and controls were randomly selected, primigravida with 20 - 24 weeks of singleton pregnancy with similar demography. Study subjects had clinical and sonographic evidence of SGA (estimated fetal weight, less than 10th percentile of the mean for that gestation). Women with hypertension, diabetes, chronic renal disease or any other medical disorder including haemoglobinopathies or any obvious fetal anomaly at the time of entry to the study, not wanting to deliver at the place of study and those who did not consent, were excluded. Controls had similar demography, but did not have clinical as well as sonographic evidence of SGA baby. Study was not about effects of therapy of anaemia (limitation), which was mainly nutritional. Study was about mothers with SGA babies, with or without anaemia and cardiac output at mid gestation and beyond. So though investigations to exclude haemoglobinopathies and other aspects of anaemia were done for exclusion, they were not part of the study. Mild and moderate anaemia cases were treated with haematics. Women with very severe anaemia during pregnancy (Hb 5 g/dL or less) always received blood transfusion, irrespective of gestation. But if Hb was around 7 gms at mid pregnancy, they were put on haematinics. If severe anaemia < 7 gms was nearing expected date of delivery blood transfusion was given.

CO (by thoracic electrical impedance plethysmography) and haemoglobin were estimated at 20 - 24 weeks, 28 - 32 weeks and 37 - 42 weeks gestation. Body mass index was also recorded. Most of the women had BMI between 20 - 25, 12.4% had BMI < 20 and the mean BMI was 21.02 + 1.57. Among the controls, in all age groups, most of the women had BMI between 20 - 25, 8% had BMI < 20 and the mean BMI was 21.44 + 1.51. In all the subgroups (FGR with mild anaemia, FGR with moderate anaemia, FGR with severe anaemia and FGR without anaemia) the difference between the mean CO of women having BMI < 20, between 20 - 25 and > 25 was statistically insignificant. In both study subjects and Controls most of the women had BMI between 20 - 25 at 20 - 24 weeks and the difference between the mean BMI of the two groups was also statistically insignificant, however in study subjects 12.2% women had BMI < 20 compared to only 8% in Controls ($p < 0.05$).

Outcome of each case included in the study, was observed and recorded. Out of all the women who presented to the outpatient, 523 were registered as per inclusion and exclusion criteria. Thirteen cases were lost after the first visit and 10 after the second visit. So, the remaining 500 women were the study subjects with 500 controls. Women with SGA at mid pregnancy with or without anaemia and controls were followed. Anaemia was defined as Hb < 11 g/dl at the time of entry to study, mild anaemia Hb - 9.0 g/dl - 10.9 g/dl, moderate Hb - 7.0 g/dl - 8.9 g/dl and severe Hb < 7.0 g/dl.

Results

Among the 500 study subjects (SGA at 20 - 24 weeks), 79.2% had anaemia compared to 63.4% anaemic cases among the controls ($p < 0.05$). The number of cases with anaemia and without anaemia amongst study subjects and controls didn't change with advancing gestation, though degree of anaemia changed as women at mid gestation with mild and moderate, severe anaemia received haematics and women with very severe anaemia (< 5 gm/100) received blood transfusions.

Of the study subjects (500), 286 (57.2%) women had CO between 5.0 - 5.49 l/min, 147 (29.4%) between 5.5 - 5.99 l/min and 67 (13.4%) between 6.0 - 6.49 l/min. The minimum CO was 5.23 l/min, maximum 6.34l/min and the mean value was 5.622 ± 0.307 l/min at 20 - 24 weeks. In the controls (500), at 20 - 24 weeks, 80 (16%) women had CO between 5.0 - 5.49 l/min, 97 (19.4%) between 5.5 - 5.99 l/min, 216 (43.2%) between 6.0 - 6.49 l /min, 72 (14.4%) between 6.5 - 6.99 l/min, 32 (6.4%) between 7.0 - 7.49 l/min and 3 (0.6%) women had CO between 7.50 - 7.99 l/min. The minimum CO was 5.37 l/min, maximum 7.67 l/min and the mean CO was 6.067 ± 0.563 l/min. The mean CO of study subjects was significantly less ($p < 0.01$) than controls at 20 - 24 weeks (Table 1).

	CO(l/min)		**5.0 - 5.49**	**5.5 - 5.99**	**6.0 - 6.49**	**6.5 - 6.99**	**7.0 - 7.49**	**7.5 - 7.99**
Study Subjects (SGA)	20 - 24 weeks	NO	286	147	67	00	00	00
		%	57.2	29.4	13.4	00	00	00
	28 - 32 weeks	NO	31	364	104	01	00	00
		%	6.2	72.8	20.8	0.2	00	00
	37 - 42 weeks	NO	71	354	05	00	00	00
		%	16.5	82.3	1.2	00	00	00
	Mean CO (Mean ± SD)		MCO1		MCO2		MCO3	
		5.622 ± 0.307 (500)		5.795 ± 0.206 (500)		5.644 ± 0.161 (500)		
Controls (AGA)	CO(l/min)		5 - 5.49	5.5 - 5.99	6.0 - 6.49	6.5 - 6.99	7.0 - 7.49	7.5 - 7.99
	20 - 24 weeks	NO	80	97	216	72	32	03
		%	16	19.4	43.2	14.4	6.4	0.6
	28 - 32 weeks	NO	00	03	178	176	137	06
		%	00	0.6	35.6	35.2	27.4	1.2
	37 - 42 weeks	NO	00	02	180	160	105	03
		%	00	0.5	40	35.5	23.3	0.7
	Mean CO (Mean ± SD)		MCO1		MCO2		MCO3	
		6.067 ± 0.563 (500)		6.730 ± 0.372 (500)		6.660 ± 0.376 (450)*		
Z test			Z >2.58, p < 0.01		Z >2.58, p < 0.01		Z > 2.58, p < 0.01	

Table 1: *CO in Study subjects and Controls.*

*1)*70 study subjects and 50 controls delivered preterm 2) Numbers in brackets indicate total women*

MCO1 - Mean CO at 20 - 24 weeks, MCO2 - Mean CO at 28 - 32 weeks, MCO3 - Mean CO at 37 - 42 weeks.

Of the study subjects (500), 31 (6.2 %) women had CO between 5.0 - 5.49 l/min, 364 (72.8%) between 5.5 - 5.99 l/min, 104 (20.8%) between 6.0 - 6.49 l/min and one (0.2%) 6.55 l/min. The minimum CO was 5.23 l/min, maximum 6.55 l/min and the mean was 5.795 + - 0.206 l/min at 28 - 32 weeks. Amongst the controls (500), 3 (0.6%) women had CO between 5.5 - 5.99 l/min, 178 (35.6 %) between 6.0 - 6.49 l/min, 176 (35.2%) between 6.5 - 6.99 l/min, 137 (27.4%) between 7.0 - 7.49 l/min and 6 (1.2 %) between 7.50 - 7.99 l/min. The minimum CO was 5.67 l/min, maximum 7.88 l/min and the mean was 6.730 + - 0.37 l/min at 28 - 32 weeks and the mean CO of controls with anaemia was significantly higher ($p < 0.01$) than women with SGA and anaemia. Likewise, the mean CO of controls with anaemia was significantly higher ($p < 0.01$) than SGA with anaemia in later weeks also. The mean CO of controls with anaemia was significantly higher ($p < 0.01$) than those with SGA baby and anaemia at 20 - 24, 28 - 32 and 37 – 42 weeks (Table 2). The mean CO in controls without anaemia was significantly higher ($p < 0.01$) than that of FGR without anaemia at 20 - 24 weeks, 28 - 32 week as well as at 37 - 42 weeks ($p < 0.01$) (Table 2).

	CO(l/min)		**5.0 - 5.49**	**5.5 - 5.99**	**6.0 - 6.49**	**6.5 - 6.99**	**7.0 - 7.49**	**7.5 - 7.99**
SGA and anaemia	20 - 24 weeks	NO	186	143	67	00	00	00
		%	46.9	36.1	16.9	00	00	00
	28 - 32 weeks	NO	16	275	104	01	00	00
		%	4.0	69.5	26.2	0.3	00	00
	37 - 42 weeks	NO	48	283	05	00	00	00
		%	14.3	84.2	1.5	00	00	00
	Mean CO (Mean ± SD)		MCO1		MCO2		MCO3	
		5.687 ± 0.312 (396)		5.836 ± 0.205 (396)		5.670 ± 0.166 (336)*		
AGA and anaemia	CO(l/min)		5 - 5.49	5.5 - 5.99	6.0 - 6.49	6.5 - 6.99	7.0 - 7.49	7.5 - 7.99
	20 - 24 weeks	NO	00	01	209	72	32	03
		%	00	0.3	65.9	22.7	10	0.6
	28 - 32 weeks	NO	00	02	22	154	133	06
		%	00	0.7	6.9	48.6	41.9	1.9
	37 - 42 weeks	NO	00	01	23	150	102	03
		%	00	0.3	8.2	53.8	36.6	1.0
	Mean CO (Mean ± SD)		MCO1		MCO2		MCO3	
		6.522 ±0.182 (317)		6.917 ± 0.330 (317)		6.836 ± 0.365 (279)*		
Z test			Z >2.58, p < 0.01		Z >2.58, p < 0.01		Z > 2.58, p < 0.01	

Table 2: *CO between Study subjects and Controls with anaemia.*

*1)*60 FGR and 38 Controls delivered preterm 2) Numbers in brackets indicate total women*

MCO1 - Mean CO at 20 - 24 weeks, MCO2 - Mean CO at 28 - 32weeks, MCO3 - Mean CO at 37 - 42 weeks.

However, the mean CO of women with SGA and` anaemia (396) was significantly greater than women with SGA without anaemia (104) at 20 - 24 weeks (p < 0.01) as well as at 28 - 32 weeks, and later (p < 0.01) (Table 3).

	CO(l/min)		**5.0 - 5.49**	**5.5 - 5.99**	**6.0 - 6.49**	**6.5 - 6.99**	**7.0 - 7.49**	**7.5 - 7.99**
SGA without anaemia	20 - 24 weeks	No.	100	04	00	00	00	00
		%	96.2	3.8	00	00	00	00
	28 - 32 weeks	No.	15	89	00	00	00	00
		%	14.4	85.6	00	00	00	00
	37 - 42 weeks	No.	23	71	00	00	00	00
		%	24.5	75.5	00	00	00	00
	Mean CO (Mean ± SD)		MCO1		MCO2		MCO3	
		5.375 ± 0.078 (104)		5.642 ± 0.119 (104)		5.549 ± 0.093 (94)*		

	CO(l/min)		5 - 5.49	5.5 - 5.99	6.0 - 6.49	6.5 - 6.99	7.0 - 7.49	7.5 - 7.99
AGA without anaemia	20 - 24 weeks	No.	80	96	07	00	00	00
		%	43.7	52.4	3.8	00	00	00
	28 - 32 weeks	No.	00	01	156	22	04	00
		%	00	0.5	85.2	12	2.2	00
	37 - 42 weeks	No.	00	01	157	10	03	00
		%	00	0.6	91.8	5.8	1.8	00
	Mean CO (Mean ± SD)		MCO1		MCO2		MCO3	
		5.751 ± 0.182 (183)		6.505 ± 0.350 (183)		6.372 ± 0.347 (171)*		
Z test			Z > 2.58, p < 0.01		Z > 2.58, p < 0.01		Z > 2.58, p < 0.01	

Table 3: *CO of Study subjects and Controls without anaemia.*

*1)*10 FGR and 12 Controls delivered preterm 2) Numbers in brackets indicate total women*

MCO1 - Mean CO at 20 - 24 weeks, MCO2 - Mean CO at 28 - 32weeks, MCO3 - Mean CO at 37 - 42 weeks

The mean CO was 5.391 ± 0.090 l/min at 20 - 24 weeks, 5.666 ± 0.129 l/min at 28 - 32 weeks and 5.570 ± 0.093 l/min at 37 - 42 weeks in women with SGA and mild anaemia (211). The mean CO was 5.959 ± 0.344 l/min at 20 - 24 weeks, 6.005 ± 0.337 l/min at 28 - 32 weeks, 5.808 ± 0.349 l/min at 37 - 42 weeks with SGA and moderate anaemia (165). The mean CO was 6.256 ± 0.319 l/min at 20 - 24 weeks, was 6.026 ± 0.180 l/min at 28 - 32 weeks and 5.863 ± 0.076 l/min at 37 - 42 weeks in cases with SGA with severe anaemia (20). Cases with SGA with severe, moderate as well as mild anaemia at 20 - 24 weeks, 28 - 32 weeks and 37 - 42 weeks gestation had significantly lower CO ($p < 0.05$). CO was inversely proportional to severity of anaemia. In controls with mild anaemia (210), the mean CO was 6.314 ± 0.194 l/min at 20 - 24 weeks, 6.761 ± 0.222 l/min at 28 - 32 weeks, 6.669 ± 0.250 l/min at term. With moderate anaemia (97), the mean CO was 6.899 ± 0.182 l/min at 20 - 24 weeks, 7.231 ± 0.237 l/min at 28 - 32 weeks and it was 7.228 ± 0.277 l/min at term. With severe anaemia (10), mean CO was 7.381 ± 0.168 l/min, at 20 - 24weeks, 7.356 ± 0.460 l/min, at 28 - 32 weeks, and 7.340 ± 0.090 l/min between 32 - 42 weeks. In controls, also there was significant difference ($p < 0.05$) between CO of mild, moderate and severe anaemia, at all gestations (20 - 24 weeks, 28 - 32 weeks and 37 - 42 weeks). It was inversely proportional to the severity of anaemia. But the mean CO in all the cases of anaemia with SGA baby was significantly lower than the cases of controls with anaemia of similar degree.

In all the cases CO was highest at 28 - 32 weeks, except in women with severe anaemia who had highest CO at 20 - 24 weeks. May be because many women with severe anaemia received blood transfusion and became moderately anaemic at advancing gestations, none had severe anaemia at 28 - 32 weeks and at term (Table 4).

	CO (l/min)	**20 - 24 weeks**	**28 - 32 weeks**	***37 - 42 weeks**
SGA and mild anaemia (211)	Min	5.32	5.34	5.32
	Max	5.76	5.98	5.98
	Mean	5.421 ± 0.090(211)	5.686 ± 0.129(211)	5.570 ± 0.093 (193)
AGA and mild anaemia (210)	Min	6.0	5.67	6.0
	Max	7.0	7.33	7.0
	Mean	6.314 ± 0.194 (210)	6.761 ± 0.222 (210)	6.669 ± 0.250 (197)
Z test		Z > 2.58, p < 0.01	Z > 2.58, p < 0.01	Z > 2.58, p < 0.01
SGA and moderate anaemia (165)	Min	5.33	5.64	5.33
	Max	6.24	6.32	6.23
	Mean	5.959 ± 0.344(165)	6.005 ± 0.337 (165)	5.808 ± 0.349(137)

AGA and moderate anaemia (97)	Min	5.98	6.04	5.57
	Max	7.34	7.54	7.99
	Mean	6.899 ± 0.182(97)	7.231 ± 0.237 (97)	7.228 ± 0.277 (80)
Z test		Z > 2.58, p < 0.01	Z > 2.58, p < 0.01	Z > 2.58, p < 0.01
SGA and severe anaemia (20)	Min	6.21	5.86	5.65
	Max	6.34	6.55	5.89
	Mean	6.256 ± 0.319 (20)	6.026 ± 0.180 (20)	5.863 ± 0.076 (06)
Aga and severe anaemia (10)	Min	7.0	5.99	7.23
	Max	7.67	7.88	7.44
	Mean	7.381 ± 0.168(10)	7.356 ± 0.460 (10)	7.340 ± 0.090 (02)
Z test		Z > 2.58, p < 0.01	Z > 2.58, p < 0.01	Z > 2.58, p < 0.01

Table 4: *CO of Study subjects and Controls with mild, moderate and severe anaemia.*

Numbers in brackets – total number of women

Min: Minimum CO; Max: Maximum CO; Mean - Mean CO

The mean CO in cases of SGA baby with mild anaemia was higher than SGA without anaemia at all gestations (20 - 24 weeks,28 - 32 weeks and 37 - 42 weeks) but the difference was not significant (p > 0.05). However, the mean CO of cases with SGA with moderate anaemia was significantly higher than cases of with SGA without anaemia at all the three gestations. There was significant (p < 0.01) difference between the mean CO of cases with SGA baby with severe anaemia and cases with SGA without anaemia, cases with SGA and severe anaemia having higher mean CO at all the three gestations (20 - 24 weeks, 28 - 32 weeks and 37 - 42 weeks).Controls with mild ,moderate and severe anaemia also had significantly (p < 0.01) higher CO than controls without anaemia at all the three gestations (20 - 24 weeks, 28 - 32 weeks and 37 - 42 weeks) (Table 5).

	Mean CO (Mean ± SD)		
	20 - 24 weeks	**28 - 32 weeks**	**37 - 42 weeks**
SGA no anaemia	5.375 ± 0.078 (104)	5.642 ± 0.119 (104)	5.549 ± 0.093 (94)
SGA and mild anaemia	5.391 ± 0.090 (211)	5.666 ± 0.129 (211)	5.570 ± 0.093 (193)
Z test	Z=1.6, p > 0.05	Z = 1.6, p > 0.05	Z = 1.7, p > 0.05
SGA no anaemia	5.375 ± 0.078 (104)	5.642 ± 0.119 (104)	5.549 ± 0.093 (94)
Sga and moderate anaemia	5.959 ± 0.344 (165)	6.005 ± 0.337 (165)	5.808 ± 0.349 (137)
Z test	Z > 2.58, p < 0.01	Z > 2.58, p < 0.01	Z > 2.58, p < 0.01
SGA no anaemia	5.375 ± 0.078 (104)	5.642 ± 0.119 (104)	5.549 ± 0.093 (94)
SGA and severe anaemia	6.256 ± 0.319 (20)	6.026 ± 0.180 (20)	5.863 ± 0.076 (06)
Z test	Z > 2.58, p < 0.01	Z > 2.58, p < 0.01	Z > 2.58, p < 0.01
AGA no anaemia	5.751 ± 0.182 (183)	6.505 ± 0.350 (183)	6.372 ± 0.347 (171)
AGA and mild anaemia	6.314 ± 0.194 (210)	6.761 ± 0.222 (210)	6.669 ± 0.250 (197)
Z test	Z > 2.58, p < 0.01	Z > 2.58, p < 0.01	Z > 2.58, p < 0.01
AGA no anaemia	5.751 ± 0.182 (183)	6.505 ± 0.350 (183)	6.372 ± 0.347 (171)
AGA and moderate anaemia	6.899 ± 0.182 (97)	7.231 ± 0.237 (97)	7.228 ± 0.277 (80)
Z test	Z > 2.58, p < 0.01	Z > 2.58, p < 0.01	Z > 2.58, p < 0.01

AGA no anaemia	5.751 ± 0.182 (183)	6.505 ± 0.350 (183)	6.372 ± 0.347 (171)
AGA and severe anaemia	7.381 ± 0.168 (10)	7.356 ± 0.460 (10)	7.340 ± 0.090 (02)
Z test	Z > 2.58, p < 0.01	Z > 2.58, p < 0.01	Z > 2.58, p < 0.01

Table 5: *CO according to degree of anaemia.*

Among controls, 22 women were diagnosed having FGR in last few days, but they remained with controls as they didn't have SGA baby at 20 - 24 weeks. All these women had AGA at 20 - 24 weeks and 28 - 32 weeks but were found to have SGA at 37 - 42 weeks, and 18 of these control cases had anaemia only 4 without anaemia at 20 - 24 weeks.

Discussion

Though there is not much of research but the relationship between FGR, anaemia and CO is obvious.

The physiological response to anaemia is a compensatory increase in CO in order to maintain adequate oxygen delivery. Low maternal CO is reported in cases of foetal growth restriction/SGA babies. However, very few studies are available about relationship of SGA baby and anaemia and maternal CO at mid gestation. Various researchers who have studied maternal cardiac function in women with SGA babies have reported that in these women, maternal cardiovascular adaptation is abnormal [6,11,12,16].

In the present study, it was revealed that at all the gestations (20 - 24 weeks, 28 - 32 weeks and 37 - 42 weeks), there was highly significant difference (p < 0.01) between the CO of study subjects (SGA baby), appropriate for gestation age (AGA)controls. Study subjects had less mean CO than controls. Also, the mean CO of women who had SGA baby and anaemia was significantly lower (p < 0.01) than controls with anaemia. Also mean CO of women with SGA baby without anaemia was significantly (p < 0.01) less than controls without anaemia, at all the three gestations. Similarly, the mean CO in women with SGA baby and mild anaemia, SGA with moderate anaemia and SGA with severe anaemia were significantly lower (p < 0.01), than the respective categories of the controls.

Rosso., *et al*. [17] carried out a study to compare the hemodynamic characteristics of 11 normotensive gravida who had SGA babies, with 11 controls with SGA babies with similar age, parity and body size. At 36 - 38 weeks of gestation, plasma volume (PV) and CO were significantly lower in SGA cases. A reduced PV lead to a lower CO and, secondarily reduced uterine blood flow and restricted foetal growth. Duvekot., *et al*. [6] did a study in which researchers examined 10 women, early in the first trimester, who subsequently had normal pregnancies and four women who subsequently developed SGA babies. They found that pregnancies complicated by SGA babies had a suboptimal increase in CO and decreased preload due to smaller left atrial diameter, and reduced PV compared to normal pregnancies. Vasapollo [12] also reported higher CO in women who had AGA babies compared with the women with SGA babies.

Bamfo., *et al.* [18] also found lower CO in the women with SGA compared to cases with AGA babies. Bamfo., *et al*. [11] later reported that in women with FGR, maternal CO was lower compared to the women with AGA baby and the difference persisted even after correction for maternal age, ethnic origin and body surface area. The most likely explanation given by the researchers was that in cases with SGA babies the preload was lower than women who did not have SGA. The lower CO in women with SGA babies was mainly due to a reduction in preload and was further suggestive of reduced plasma volume expansion [19].

There is increase in CO in cases of anaemia in normal pregnancy. However, in pregnancy with SGA, the rise in CO is hampered. In another study CO of 500 pregnant women was measured at six different gestations [20]. Women with anaemia had significantly higher CO than those with normal haemoglobin, the rise in CO was inversely proportional to low haemoglobin. Of the women having CO in the lesser range, 80% developed SGA later. These facts are contradictory and raise an important question as to what happens to CO in women who have SGA baby as well as anaemia, whether CO is more as in cases of anaemia or less as seen cases in cases with foetal growth restriction.

In the present study of cases at mid gestation with SGA baby and anaemia, the mean CO was significantly higher than cases with SGA baby but no anaemia throughout. The mean CO in women with FGR and mild anaemia was more than cases with SGA baby but no anaemia, but the difference was insignificant. The mean CO in cases with SGA baby and moderate anaemia and SGA baby with severe anaemia were significantly higher than cases of SGA baby without anaemia throughout. Also, there was significant difference between the mean CO in cases with SGA baby and mild, moderate and severe anaemia at all the three gestations, the mean CO increasing with the severity of anaemia. There was significant difference between the mean CO of controls also with mild, moderate and severe anaemia at all the three gestations, the mean CO increasing with the severity of anaemia.

Though the mean CO of study subjects with anaemia was significantly higher than study subjects without anaemia, it was significantly lower than controls with similar severity of anaemia. Anaemia is a high output state. The physiologic response to anemia is a compensatory increase in CO in order to maintain adequate oxygen delivery, the extent of this response appears to be closely related to the decrease in hematocrit but this response seems to be less in women with SGA babies [21,22].

The mean CO of women having both SGA babies and anaemia was significantly higher than SGA babies without anaemia but was significantly less than controls with anaemia throughout pregnancy. The mean CO in cases of FGR and mild anaemia was almost similar to cases with SGA babies without anaemia but was significantly lower than controls with mild anaemia. The mean CO in cases with SGA babies with moderate anaemia and SGA babies and severe anaemia was significantly higher than FGR without anaemia but significantly less than controls with moderate anaemia and severe anaemia respectively. The mean CO was higher in women having SGA babies and anaemia, compared to non - anaemic women with SGA babies, but was lower than those with women with AGA fetus with similar severity of anaemia. Various researchers, who have studied maternal cardiac function in relation to foetal growth, have reported that in these women, the maternal cardiovascular adaptation was abnormal [6,11,12,17]. Hence these women were not able to have sufficient rise in CO in response to anaemia. Duvekot., *et al*. [6] also reported that in pregnancies with problems in foetal growth, the maternal cardiovascular adaptation is abnormal with reduced plasma volume and a suboptimal increase in CO in response to triggering factors. In the present study, in the study subjects (SGA) and controls (AGA), the mean CO of women with anaemia were significantly ($p < 0.01$) higher than those without anaemia throughout. Women with SGA and mild anaemia didn't have a significant increase in CO, but caused a significant increase in CO among controls with mild anaemia. The mean CO of women with moderate anaemia, severe anaemia were significantly higher than those without anaemia throughout, in the study subjects as well as controls but with significant difference between the mean CO of women with mild, moderate and severe anaemia in the study subjects as well as the controls with the mean CO increasing with the severity of anaemia. Although mean CO was higher in women having SGA and anaemia compared to non - anaemic women with SGA, it was less than what it was in controls with similar severity of anaemia. Present study concentrated mainly on SGA baby, anaemia and CO at mid gestation and outcome. It did not go in details of anaemia therapy, which surely affected the haemoglobin status in last few days of pregnancy and is the weakness of the study.

There are studies about CO and feotal growth and anaemia and foetal growth, but not many with foetal growth, anaemia and CO measured at mid gestation. So, it was decided to look into the issue, the strength of the study.

Conclusion

Anaemia caused a significant increase in CO in women with SGA but their CO was significantly lower than women with AGA baby, having similar severity of anaemia. From the results of the present study as well as from the studies done by other researchers, increase in CO seen in normal pregnancy is hampered in women with SGA babies. Anaemia further complicates the effect. More studies are needed.

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Declaration of Interest Statement

The authors report no conflict of interest.

Impact Statement

What is already known about the subject

Cardiac output increases from early pregnancy. If this is impeded, placental circulation is affected, and so the fetal growth. Pregnancies with FGR lack stimulus for hemodynamic changes. Further heart responds to anaemia by increased CO to maintain adequate oxygen delivery. Anemia by causing hypoxia, iron deficiency, by increasing serum norepinephrine induce maternal fetal stress, which stimulates synthesis of corticotropin - releasing hormone (CRH), which increases fetal cortisol production, likely to inhibit fetal growth. Anemia leads to FGR. Physiological response to anemia is compensatory increase in CO. Maternal CO is less in women who have FGR. These contradictions raise important question, about happenings in cases of mid-gestation FGR and anaemia. So, it was decided to look into.

The results of the study add

Mean CO of women with mid-gestation FGR and anaemia was significantly greater than women with FGR without anaemia throughout, highest at 28 - 32 weeks. But CO was significantly less than non - FGR women with similar severity of anaemia. Women with no FGR and anaemia had significantly more increase in CO throughout than no FGR without anaemia.

The implications of these findings for clinical and further research

Results of present study reveals that, rise of CO is hampered in women with FGR even with anaemia. FGR can occur in last few weeks too in anaemic women. It is essential to do more research.

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