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Mid Pregnancy Fetal Growth Restriction and Maternal Anaemia a Prospective Study

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Abstract

Background: Fetal growth restriction (FGR) in anaemic women leads to high perinatal morbidity, mortality and long term sequelae too.

Objective: Was to know relationship between mid gestation FGR, maternal anaemia and neonatal outcome.

Materials and methods: Case control study was done in 500 study subjects with special criteria (primigravida with FGR at midgestation with or without anaemia, no other disorders), 500 controls were with similar criteria without FGR.

Results: Of 500 study subjects with FGR at 20-24 weeks, 79.2% were anaemic, (53.3% had mild, 41.7% moderate, 5% severe anaemia), 20.8% nonanaemic. Amongst controls, 63.4% were anaemic, (66.2% mild, 30.5% moderate, 3.15% severe), 36.6% nonanaemic. Significantly more study subjects were anaemic, (moderately, severely) with 2.2 times more chances of anaemia in study compared to controls. 7.2% with mild, 14.5% with moderate, 43.9% with severe, 5.5% without anaemia had preterm birth, significant increase in preterm births with increasing severity of anaemia. There was significant ($p<0.05$) difference between mean birth weight. MBW decreasing with anemia severity. Risk for LBW, VLBW in mild, moderate, severe anaemia was 1.2 and 1.7, 3.8 and 1.5, and 1.9 and 4.2 respectively, MBW of study cases with mild anaemia was, (2085.72 ± 317.2 g), with moderate MBW, (1950.26 ± 410.3 g), with severe (1380.25 ± 480.1 g), without anaemia (2146.42 ± 279.1 g), significant difference in moderate and severe anaemia cases ($p<0.01$). None with anaemia at 20-24 weeks became nonanaemic with increasing gestation.

Conclusion: FGR at midgestation is significantly associated with anaemia in mother, risk of FGR increases with severity of anaemia. With FGR and anaemia risk of preterm pains, preterm births increase with increase in severity of anaemia MBW decreases. In day to day practice women with anaemia at mid gestation do not become nonanaemic. In anaemic women, FGR can occur in later weeks of pregnancy also.

Keywords: Fetal growth restriction, Haemoglobin, Diabetes, Hypertension

Introduction

Fetal growth restriction (FGR), estimated fetal weight less than 10th percentile of mean for that gestation is known to increase perinatal morbidity and mortality and long term sequelae too. It is estimated that 13.7 million FGR infants are born annually, comprising of 11% of births in developing countries. Maternal anaemia is reported to be one of the commonest maternal causes of FGR. Various studies reveal that anaemia (Hb<11 g/dl), particularly iron deficiency anaemia, significantly increases the chances of FGR. Anaemia, by causing hypoxia and iron deficiency by increasing serum norepinephrine concentration induce maternal and fetal stress, which stimulates the synthesis of corticotropin-releasing hormone (CRH). CRH increases fetal cortisol production, which is likely to inhibit foetal growth. Also, iron deficiency is believed to increase the oxidative damage of erythrocytes and the fetoplacental unit. However there are not many studies from resource poor regions about FGR in mid gestation and anaemia in the mother. Present study was done to know the relationship between FGR at midgestation, maternal anaemia and neonatal outcome.

Materials and Methods

Case control, prospective study was carried out in obstetrics gynaecology of a rural referral hospital in central India after approval of institute's ethics committee. Study subjects were primigravida with singleton pregnancy of 20-24 weeks with FGR [1-3] (clinical, by clearly known last menstrual period (LMP) [4-6] in women with previous regular cycles, uterine fundal height and sonographically estimated fetal weight less than 10th percentile of the mean for that gestation). While Doppler studies were done in some, not in all because of the cost involved and are not part of the study [7]. Clinical (by LMP, uterine height) and sonography, both were used. In case of discrepancy with sonography consensus was reached in all cases after putting everything in proper perspective. Women with hypertension, diabetes, renal, cardiac disease or obvious anomaly in the baby at the time of entry to study [8-10], and smokers were not included. Body mass index

(BMI) was recorded in study subjects and controls BMI. As per the study criteria 523 women could be recruited. Informed consent was taken in all cases.

Haemoglobin was estimated at entry between 20-24 weeks and repeated at 28-32 weeks and 37-42 weeks of pregnancy. Cases with haemoglobinopathy were excluded. For diagnosis of anaemia, haemoglobin less than 11 g/dl was further divided into mild Hb-9.0 g/dl-10.9 g/dl, moderate 7.0 g/dl- 8.9 g/dl and severe <7.0 g/dl). Thirteen women were lost after the first visit, 10 after the second visit, so 500 women became the study subjects. Five hundred cases without clinical or sonographic evidence of FGR [11-17] at the time of entry to study and with similar criteria were enrolled as controls. Detailed history general, systemic, obstetric examination were recorded and all the women were followed till 7 days post partum. Statistical analysis was done by EPI- info 6 software. Z test, Analysis of variance (ANOVA) and univariate analysis were used for analyzing the data.

Results

Of the 500 study subjects (primigravida with FGR at 20-24 weeks), 396 (79.2%) were having anaemia compared to 317(63.4%) controls (women with appropriate for gestational age (AGA) foetus at 20-24 weeks), difference significant ($p<0.05$). Of the study subjects, 327 (65.4%) and of controls 299 (59.8%) were rural, difference insignificant ($p = 0.76$). The mean age of the study subjects was 23.47 ± 2.30 years and mean age of the controls was also 23.53 ± 1.99 years. Three percent women with FGR and anaemia and 1.2% control cases with anaemia were of less than 20 years of age, difference insignificant ($p= 0.62$). Amongst study subjects with anaemia, youngest was 18 years, eldest 32 years and the mean was 23.35 ± 2.23 years. Amongst controls with anaemia also youngest was 19 years, eldest 32 years and the mean age was 23.50 ± 1.81 years. One percent cases of FGR without anaemia and 1% controls without anaemia were ≤20 years, youngest was 19 years, eldest 32 years, the mean age was 23.92 ± 2.53 years in study subjects and the youngest was 19 years, eldest 32 years and the mean age was 23.60 ± 2.28 years in controls without anaemia (Table 1 and Figure 1).

Of the 396(79.2%) anaemic study subjects, 211 (53.3%) were having mild, 165 (41.7%) moderate, 20(5%) severe anaemia and only 104 (20.8%) were nonanaemic at mid gestation. Of controls with anemia [317 (63.4%), 210 (66.2%)] were mildly anaemic, 97(30.5%) moderate, 10 (3.15%) severe anaemiac and 183(36.6%) were nonanaemic at mid gestation.

	Degree of anaemia	20-24 weeks			28-32 weeks			37-42 weeks		
		Total	%	%*	Total	%		Total ***	%	%**
FGR with Anaemia	Mild	211	53.3	42.2	211	53.3	42.2	193	57.4	44.9
	Moderate	165	41.7	33	165	41.7	33	137	40.8	31.9
	Severe	20	5	4	20	5	4	6	1.8	1.3
	Total	396	100	79.2	396	100	79.2	336	100	78.1
FGR without Anaemia		104	20.8		104	20.8		94	21.9	
Total		500	100		500	100		430	100	
Controls with Anaemia-317	Mild	210	66.2	42	210	66.2	42	197	70.6	43.8
	Moderate	97	30.5	18.4	97	30.6	19.4	80	28.7	17.8
	Severe	10	3.15	2	10	3.1	2	2	0.7	0.4
	Total	317	100	63.4	317	100	63.4	279	100	62
Controls without Anaemia		183	36.6		183	36.6		171	38	
Total		500	100		500	100		450	100	

*% out of 500

** % out of 430 in FGR and 450 in Controls

***Total number and % are less in each group as remaining women delivered preterm

Table 1: Anaemia in Study subjects and Controls at different gestations.

Amongst study subjects significantly ($p<0.01$) more study subjects were moderately anaemic (41.7%) than controls (30.5%) and also more study subjects were severely anaemiac (5.0%) than controls (3.15%), difference was significant ($p=0.093$) (Figure 1).

Amongst women who had FGR and anaemia (396), 335 (84.6%) had BMI between 20-25, and 58 (14.6%) less than <20. Amongst controls with anaemia (317), 282(89%) had BMI between20-25 and 29(9.1%) had BMI<20, difference significant ($p<0.05$). Three (0.8%) study subjects and 6(1.9%) controls had BMI>25. The mean BMI of study subjects with anaemia was 20.86 ± 1.48 and of controls with anaemia was 21.36 ± 1.48. Amongst study subjects without anaemia, 95 (91.3%) had BMI between 20-25, 4(3.9%) <20 and 5(4.8%)>25 and the mean BMI was 21.60 ± 1.76. Amongst controls without anaemia, 168 (91.8%) had BMI between 20-25, 11(6%) <20 and 4(2.2%)>25, and mean BMI was 21.58 ± 1.55. The mean BMI of study subjects without anaemia

was 21.60 ± 1.76 and of controls without anaemia was 21.58 ± 1.55, difference insignificant (p=0.58).

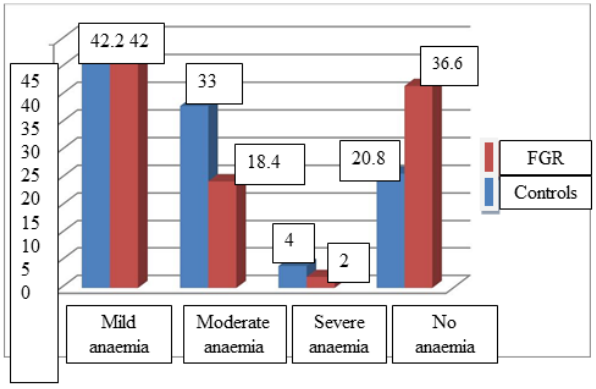

Figure 1: Anaemia in study subjects and controls at 20-24 weeks.

It was revealed that in FGR cases degree of mild, moderate, severe anaemia changed with advancing gestation with increase or decrease in haemoglobin (Figure 2). Of 211 cases of FGR with mild anaemia at 20-24 weeks, 7(3.3%) became moderately anaemic at 28-32 weeks, 3 of these 7 had preterm birth, remaining 4 delivered at term. Four (1.9%) women with mild anaemia at 20-24 weeks as well as 28-32 weeks became moderately anaemic at term. Of 165(41.7%) women with moderate anaemia at 20-24 weeks, 4(2.4%), became mildly anaemic at 28-32 weeks and continued to be mildly anaemic till term. Six (3.6%) women with moderate anaemia at 20-24 weeks as well as 28-32 weeks became mildly anaemic at term. All 20(100%) women with severe anaemia at 20-24 weeks became moderately anaemic at 28-32 weeks, 14 (70%) of them delivered preterm and 6(30%) continued to be moderately anaemic till term.

Of 20(100%) women with severe anaemia, 18(90%) received blood transfusion. Study was about mid gestation FGR and anaemia in primigravida with no other disorders and neonatal outcome. It was not meant to study types and efficacy of therapy but what happens to anaemic, nonanaemic women in busy every day practice was recorded. None of the women with anaemia at 20-24 weeks became nonanaemic with increasing gestation.

In control, cases with anaemia, also the number of women with mild, moderate, severe anemia changed with advancing gestation, with increase or decrease in haemoglobin. Of 210 (66.2%) controls with mild anaemia at 20-24 weeks, 5(2.4%) became moderately anaemic at 28-32 weeks, one (20%) of them delivered preterm. Four (1.9%) of 210 women having mild anaemia at 20-24 weeks as well as 28-32 weeks became moderately anaemic at term. Of 97 women with moderate anaemia at 20-24 weeks, 94(96.7%) continued to be moderately anaemic at 28-32 weeks and 3 (3.3%) became mildly anaemic by term. All 10(3.15%) control cases with severe anaemia at 20-24 weeks became moderately anaemic by 28-32 weeks, 8(80%) delivered preterm and 2(20%) remained moderately anaemic till term.

Mildly anaemic cases were equal in study subjects (42.2%) and controls (42%), but significantly more study subjects (33%) were moderately anaemic than controls (19.4%), and also severely anaemic, 4.0% study subjects and 2.0% controls. Moderate and severe anaemia in primigravida with no medical disorders were significantly associated with FGR at 20-24 weeks (Figure 3).

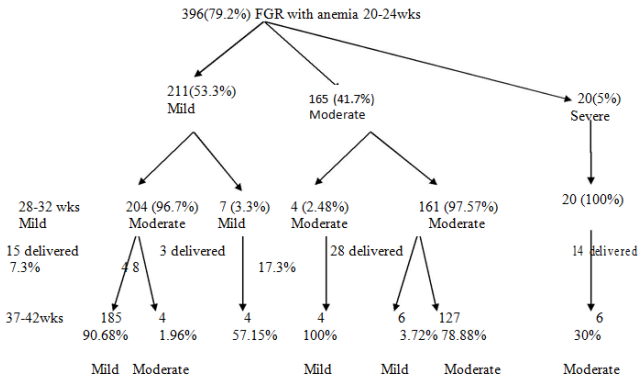

Figure 2: Change in degree of anaemia with advancing gestation in FGR with anaemia.

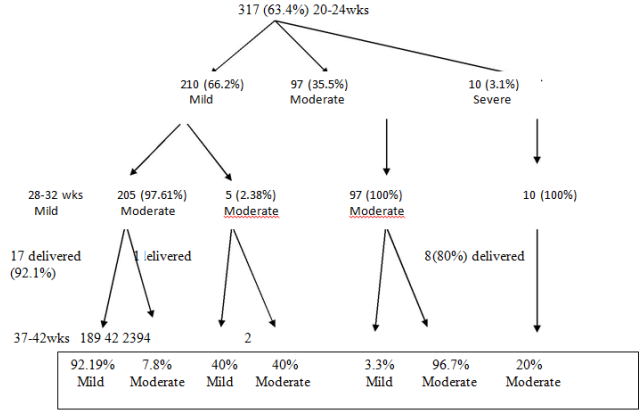

Figure 3: Change in degree of anaemia with advancing gestation in Controls with anaemia.

Since the study was in primigravida with no other disorder, there were no preterm inductions. Of nineteen (9% of 211) study subjects with mild anaemia, who had preterm pains, in 4 (21%) preterm birth could be arrested and 15(79%) had preterm births. So of 211 study subjects with mild anaemia, preterm births were 15(7.1%). Amongst moderate anaemia with FGR, 29 (17.5%of 165) had preterm pains, in 10(34.5%) preterm birth was arrested and 19(11.51% of 165) had preterm birth. Of 20 women with severe anaemia and FGR, 14 (70% of 20) had preterm pains, in 6(42.86%) preterm birth was arrested and 8(57.14%) had preterm births. Of study subjects, without anaemia (104), 13 (12.5%) had preterm pains, preterm birth was arrested in 5(38.5% of 13), rest 8 had preterm births. Overall of 104, nonanemic study subjects 7.7% had preterm births. Arrest of preterm birth with tocolytics decreased from 22.7% in women without anaemia to 12% in women with mild anaemia, 8.8% moderate anaemia ($p<0.05$). A total of 7.2% study subjects with mild anaemia, 14.5% with moderate anaemia, 40% with severe anaemia and 5.5 % without anaemia had preterm birth, significant increase in preterm birth with increased severity of anaemia ($p<0.05$).

Vaginal and cesarean births were almost in equal numbers with mild, moderate and no anaemia but more women with severe anaemia had vaginal births, probably because more had preterm births.

Amongst controls 22 babies (4.4%of 500), (18 mothers with anaemia (81.8%) and 4 without anaemia (18.18%) at 20-24 weeks) were found to have FGR at term though they didn't have FGR at 20-24 weeks. Of study subjects with mild anaemia (211), 2(0.9%) babies weight was <1000 g, 11(5.2%) between 1000-1499 g, 49 (23.3%) between 1500-1999 gms and 149 (70.6%) between 2000-2499 gms. The minimum and the maximum birth weight were 942 and 2476 g respectively and the MBW was 2085.72 ± 317.2 gms, none had 2.5 kg or more birth weight. Amongst study subjects with moderate anemia (165), 5 (3%) babies weight was <1000 g, 18 (11%) between 1000-1499 g and 76 (46%) between 1500-1999 gms and 66(40%) between 2000-2499 gms. The minimum and the maximum birth weight were 743 gms and 2488 g respectively and the MBW was 1950.26 ± 410 gms, no baby had weight 2.5 kg or more. Of study subjects with severe anaemia (20), 3(15%) babies had weight<1000 and 11(55%) between 1000-1499 g, 3(15%) between 1500-1999 g and 3(15%) between 2000-2499 gms, 85% babies had weight less than 2 kg. The minimum and the maximum birth weight were 903 g and 2364 gms respectively and the MBW was 1380 ± 480.1 gmsAmongst study subjects without anaemia (104),one (1%) baby was of less than <1000 gms, 3(2.8%) between 1000-1499 gm and 21(20.2%) between 1500-1999 gms, 79(76%) were between 2000-2499 gms and 24% less than 2 kg, the minimum and the maximum birth weight were 985 g and 2485 g respectively and the MBW was 2146.42 ± 279.1 gms. There was significant ($p<0.05$) difference between the MBW of the babies of the study subjects, with mild anemia, moderate anemia, and severe anemia and without anemia, the MBW increasing with the increase in hemoglobin. The risk for LBW and VLBW in women with mild, moderate and severe anemia was 1.2 and 1.7, 3.8 and 1.5, and 1.9 and 4.2 respectively. The difference between the MBW of study cases with mild anemia (2085.72 ± 317.2 g) and of those with no anemia (2146.42 ± 279.1 g) was insignificant ($p>0.05$), but with moderate anemia (1950.26 ± 410.3 gms) and of those with FGR without anemia (2146.42 ± 279.1 g) was significant ($p<0.01$). MBWof FGR with severe anemia (1380.25 ± 480.1 g) and FGR without anemia (2146.42 ± 279.1 g), significant difference. No woman with FGR at midgestation had baby weight 2.5 kg or more baby.

In FGR with mild anaemia (211), there were 14(6.6%) congenitally anomalous babies, out of which 1 with diaphragmatic hernia died. Thirty two babies (15.1%) were admitted in NICU for various reasons including one with imperforate anus, one with diaphragmatic hernia and one with sacral pit. There were 8 (3.8% of 211) neonatal deaths including one baby with diaphragmatic hernia. In FGR with moderate anaemia (165), there were 10(6% of 165), congenitally anomalous babies, of which 1 with tracheoesophageal fistula (TOF) died within 2 hours and one with duodenal atresia was operated and died on 4th day. Twenty five babies (15.1%) were admitted to NICU for various reasons including duodenal atresia and TOF, (ventricular septal defect) VSD. There were 6 (3.6%) NND including duodenal atresia and TOF.

In FGR with severe anaemia (20), there were 2(10%) congenitally anomalous babies. 14 babies (70%) were admitted in NICU for various reasons. There were 2 (10%) NND.

In women with FGR baby without anaemia, there were 6(5.8%) congenitally anomalous babies including Atrial septal defect, of which one with duodenal atresia was operated but died on 5th day. Over all 16 babies (15.4%) were admitted in NICU for various reasons. There were 3 (2.9%) NND.

Overall neonatal mortality was 3.8% in FGR with mild anemia, 3.6% in FGR with moderate anemia, 10% in FGR with severe anemia and 2.9% in FGR with no anemia.

Foetal anomalies were part of exclusion criteria but these anomalies were not diagnosed at entry to study and were detected after birth.

Discussion

A prospective study of women with FGR at mid pregnancy was carried out with 500 study subjects and equal controls to know the relationship between FGR at mid pregnancy with maternal anemia and neonatal outcome. Anaemia was significantly associated with FGR at 20-24 weeks. The risk of FGR increased with severity of anaemia. Ronnenberg et al. [18] reported that both mild and moderate anaemia are significantly associated with birth weight less than normal at all gestations. Iron-deficiency anemia alone was associated with a 242 gms less MBW. Earlier Scholl et al. [19] have reported that anaemia diagnosed early in pregnancy is associated with increased risk of LBW and preterm delivery. In some other studies, maternal iron deficiency anaemia diagnosed at entry to prenatal care was associated with low dietary energy and iron, inadequate gestational weight gain, and two fold or greater increase in the risk of preterm delivery and LBW [14,20,21].

Primigravida with no medical disorders except FGR with anaemia. In the present study of FGR at midgestation in primigravida with no other disorders (other than anemia), mild anaemia was in 42.2% study subjects, and in 42% controls also. Most of the women were of 20-29 years, with insignificant difference in the mean age of study subjects (FGR) and controls (AGA), 2.6% study subjects and 1.2% controls were <20 years (insignificant difference). In study subjects as well as controls, most of the women had BMI between 20-25 at 20-24 weeks. Difference between the mean BMI of study subjects and controls was also insignificant, however in study subjects 12.2% women had BMI<20 compared to only 8% controls, significant difference ($p<0.05$). Finally it is overall malnutrition, body size BMI and anaemia which go together. Ronnenberg et al. [22] studied the relationship between prepregnancy BMI and birth outcomes and reported that all measures of infant growth increased with increasing maternal BMI until a plateau was reached at a BMI of 22-23 kg/m^2. Infants born to the 27% of women who had BMI ≤ 18.5 kg/m^2 were at increased risk for small for gestational age (SGA) babies compared with a normal BMI, reduction of 219 ± 40 g in infant birth weight and 6.7 ± 1.3% in the birth weight ratio and an 80% increase in risk of SGA.

In the present study, in women with FGR as well as those with AGA weight (controls), there was no significant change in the degree of anaemia with advancing gestation except in the women with severe anaemia who received blood transfusion. Present study was about FGR between 20-24 weeks and relation to haemoglobin. It was not meant to study the therapy of anaemia or change in severity of anaemia with advancing gestation but this observation does reveal what happens in everyday practice. It is essential to prevent and treat anaemia preconception so that FGR due to anaemia is prevented as women with FGR were more often anaemic. Also those who are anaemic at mid gestation were more prone to give birth to LBW. Others also report the same [14,23,24]. Further even if, there was no FGR at mid gestation in women with anemia, FGR occurred later. Amongst controls 22(4.4% of 500), (18 with anaemia (81.8%) and 4 without anaemia (18.18%) at

20-24 weeks) were found to have FGR at term, with no FGR at 20-24 weeks. Monitoring is important as anaemia keeps on affecting the baby at later gestation also.

There was significant increase in preterm birth with increased severity of anaemia. Arrest of preterm birth with tocolytics decreased with severity of anaemia. The number of women who had preterm pains was high (45%) with severe anaemia. Vaginal and cesarean births were almost similar in women with mild, moderate and no anaemia. More women with severe anaemia had vaginal births probably because of more preterm births in these women. Since the study is in primigravida with no medical disorders, so there were no indications for CS in preterm labour in severe anaemia.

Lone et al. [14] have investigated the relationship between maternal anaemia and perinatal outcome in a cohort of 629 pregnant women in a tertiary care hospital in Pakistan, of which 313(49.76%) were anaemic. Haemoglobin was measured in the first antenatal visit in first trimester, at 28 to 32 weeks, at 33 to 37 weeks and in labour. The risk of preterm birth and FGR babies among the anaemic women was 4 and 1.9 times more respectively than the non-anaemic women. In a study by Levy et al. [23], higher rates of preterm birth and FGR were found among women with anemia in early pregnancy compared to the non-anemic women and maternal anemia was an independent risk factor for preterm delivery as it was a selective group. In the present study inclusion criteria was mid gestation onwards and preterm birth related to severity of anaemia were analyzed. In a study by Kidanto et al. [21], a total of 1 174 anaemic and 547 non-anaemic women, the prevalence of anaemia and severe anaemia was 68% and 5.8%, respectively. The risk of preterm birth increased significantly with the severity of anaemia. The corresponding risks for LBW and VLBW were 1.2 and 1.7, 3.8 and 1.5, and 1.9 and 4.2 respectively. In the present study, the difference between the MBW of the babies of women with FGR and moderate, severe anaemia and those without anaemia was significant. Kozuki et al. [25] also reported that moderate to severe, but not mild, maternal anemia have an association with SGA baby. Ren et al. [24] reported that low first-trimester haemoglobin increases the risk of LBW, preterm birth and SGA. Bondevik et al. [20] reported that severe maternal anemia, particularly in the first trimester, was significantly associated with adverse pregnancy outcome. Low maternal age, height or BMI also increased the risk of LBW.

From the results of the present study as well as from studies done by other researchers, it is evident that anaemia is rampant and anaemia at mid gestation has significant association with FGR, preterm pains, tocolytic efficacy, affecting overall neonatal outcome.

Conclusion

Anaemia at 20-24 weeks is significantly associated with FGR, risk increasing with the severity of anaemia. The risk of preterm pains and preterm births in women with FGR increases with increase in severity of anaemia.

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