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Research Article

Trimester Related Reference Interval Limits for Hematological Parameters for Pregnant Women of Taita-Taveta Country, Kenya

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Abstract

Hematological parameters reference intervals for pregnant women are different from those of non-pregnant women and are used to assess their health status; they vary in different populations. There is therefore a need for medical laboratories to develop local reference intervals for hematological parameters using the local population. This study was therefore carried out in order to develop 95% reference intervals for hematological parameter for pregnant women from Taita-Taveta County, Kenya. This was a cross-sectional study design involving 296 participants, 124 in their second trimester and 172 in their third trimester recruited while attending their antenatal clinics at Moi subcounty hospital, Voi, from the 16th week of pregnancy. Five milliliters of venous blood was drawn from each of the participants and subjected to full hemogram analysis using a Coulter Counter Analyzer standardized by a 4C plus control blood. Reference intervals were developed using the EP28 A3c guide. Trimester independent reference intervals were developed for RBC (x1012/L), HB (g/dL), MCH (pg), MCHC (g/dL), MCV (fL), RDW-CV (%), RDW-SD (%), WBC (x109/L), NEU (x109/L), NEU (%), LYM (x109/L), LYM (%), MON (x109/L), MON (%), BAS x109/L, EOS (x109/L), EOS (%), PLT (109/L), PCT (%), PDW (%) and MPV (fL) and trimester dependent reference intervals were developed for BAS (x109/L), BAS % and PVC (%). In conclusion, the developed trimester specific reference intervals for hematological parameters which are different from those reported in medical literature can be adopted and used for diagnosing diseases associated with pregnancy in Taita-Taveta-County, Kenya.

Keywords: Hematological parameters, Trimester specific, Reference intervals, Pregnant women, Taita-Taveta County, Moi Subcounty Hospital, Voi

Introduction

Reference intervals for hematological parameters for pregnant women are clinically used for many purposes including assessment of healthy status, progression of disease, monitoring response to therapy, or monitoring adverse reaction to new therapy during clinical trials [1]. These parameters are affected by age, gender, gestational age of pregnancy, dietary habits (nutritional status), lifestyle (smokers or non-smokers, alcoholics or non-alcoholics, active or sedentary), health status, ethnicity, genetics, geographical location (altitude above sea level), environment, instrumentation and reagents used, and the comprehensiveness of the inclusion criteria [2]. Complete and standardized hematological reference intervals for pregnant women in most sub-Saharan African countries including Kenya are limited; they do not span the three trimesters of pregnancy. The pregnancy affected hematological parameters include red blood cells and hemoglobin and their related indices, white blood cells and differential white blood cell count, and platelets and their related indices [2-4]. However, these hematological changes do not demonstrate a common trend; they vary from country and/or region to region [2,3,5-7]. Pregnancy is associated with anatomical, physiological, biochemical, and endocrine changes which affect multiple organs in order to allow the woman to adapt to the pregnant state and allow the fetus to grow and survive. Further, in most Kenyan clinical laboratories, the reference intervals for hematological parameters used to interpret laboratory results for pregnant women are those for European and North American pregnant women or those for non-pregnant women which are inappropriate. These European and North American pregnant or non-pregnant women reference intervals are sometimes different from other populations of the rest of the world. For reference intervals for hematological parameters for pregnant women to be reliable and accurate, the International Federation of Clinical Chemistry recommends that each Clinical Laboratory should develop their own reference intervals using their local population. The aim of this study was therefore to develop trimester specific 95% reference intervals for hematological parameters for pregnant women of Taita-Taveta County, Kenya and compare them with those reported in medical literature.

Materials and Methods

Study Site

This study was carried out at the Department of Clinical Chemistry, Moi Subcounty Hospital, Voi, Kenya between May 2015 and December 2017.

Study Design

This cross-sectional study involved 296 healthy pregnant women randomly recruited in their second and third trimester on commencing antennal clinic in the 16th week. The level of twenty-three hematological parameters were measured. To minimize bias, at least ten pregnant women were recruited weekly.

Study Population

The 296 healthy pregnant women, comprised of 124 in their second trimester and 172 in their third trimester registered to attend Moi Subcounty Hospital antenatal clinics from the 16th week of pregnancy after meeting the inclusion criteria. Gestational age was estimated through Ultrasonography, and the delivery day recorded in the antenatal clinic booklet.

Inclusion and Exclusion Criteria

The study included pregnant women who met the following criteria: those who consented to participate by signing a consent form, pregnant women in their second and third trimester with no history of smoking, alcohol consumption, high blood pressure, diabetes mellitus, and no previous history of taking parallel medications like antituberculosis, and antiretroviral drugs. Pregnant mothers on anti-malarial and mineral and vitamin supplements were also included in the study. The study excluded pregnant women who did not consent to participate in the study, pregnant women who were smoking, hypertensive, and alcoholics. Also excluded were pregnant women with diabetes mellitus, malaria, syphilis, HIV/AIDS, and hepatitis B and C. Absence of syphilis, HIV/AIDS, and hepatitis B and C were confirmed by running serum samples in the Clinical Laboratory, while the absence of other diseases was obtained through physical and clinical examination and history by a physician, and self-reporting using a questionnaire.

Collection of Blood Samples for Routine Serum Biochemistry Analytes

Five millilitres of venous blood was drawn with a five milliters syringe from each of the 296 pregnant women into EDTA vacutainer tubes labeled with the study number and participants name, gently swirled for half a minute to mix the blood with EDTA to prevent the sample from clotting for hematological analysis. Measurements for the twenty-three hematological parameters was performed using a Coulter Counter Analyzer standardized by a 4C plus control blood.

Estimation of the Level of Hematological Parameters

Red blood cells (RBC), hemoglobin (HB), packed cell volume (PCV), mean cell hemoglobin (MCH), mean cell hemoglobin concentration (MCHC), mean cell volume (MCV), red cell distribution width (RDW-SD), red cell distribution width (RDW-CV), white blood cells (WBC), neutrophils (NEU), lymphocytes (LYM), monocytes (MON), eosinophils (EOS), basophils (BAS), platelets (PLT), plateletcrit (PCT), platelet distribution width (PDW), and mean platelet volume (MPV) measurements were carried out using a Coulter Counter Analyzer (Coulter Ac T diff, Beckman Coulter, Miami, FL) standardized by a 4C plus control blood.

Quality Control (QC)

One quality control material was used for hematological parameters to verify the performance of the analytical process during the study period. The QC material was either ready to use or in lyophilized form. Those that were lyophilized were reconstituted as per manufacturer's instructions. The prepared quality control material was used to perform internal quality control assessment any time the study procedures were being undertaken [8].

Data Management and Statistical Analysis

For each participant, data for the two trimesters was initially recorded into a laboratory notebook, then entered into the Excel spreadsheet and cleaned. The clean data was exported to SPSS software version 21 for statistical analysis. Data was initially subjected to normality tests using mean, median, mode, skewness and kurtosis. Since the normality tests indicated that the data was non-parametric, the data was expressed in terms of median and range (Table 2). Reference intervals were developed based on CLSI (EP28 A3c) (2010) guideline that recommends the use of 2.5 and 97.5 percentiles [9]. Statistical comparisons of the median value of each of the measured analytes for the two trimesters was carried out using Mann-Whitney U Test. A two-sided ρ-value of ≤ 0.05 was considered significant. The developed reference intervals were subsequently compared with reference intervals reported in medical literature for other populations.

Ethical Approval

This study was approved by Kenyatta University Ethical Committee Ref Number I84/31987/15/ NACOSTI Ref number 16/22096/14531, Taita-Taveta county Medical director.

Results

Results for Commercial Quality Control Material for Hematological Parameters

The results of commercial quality control materials for the hematological parameters are reported in Table 1. Results indicate that the Coulter Counter Analyzer standardized by 4C plus control blood was operating within the specified requirements. All the quality control hematological parameters fell within the expected values.

Table 1: Results for the commercial quality control materials for hematological parameters

Parameter (unit)	Assigned QC report			Study QC report		
HB (g/dL)	Upper Limit	Target	Lower limit	Mean	SD	CV (%)
RBC (x1012/L)	23.50	15.50	7.50	15.48	0.14	0.90
PCV (%)	5.13	4.83	4.53	4.875	0.069	1.42
MCH (pg)	0.75	0.51	0.27	0.51	0.008	1.57
MCHC (g/dL)	34.6	32.1	29.6	31.75	0.36	1.13
MCV (fL)	33.4	30.4	27.4	29.87	0.37	1.24
RDW-SD (%)	110.5	105.5	100.5	106.33	0.87	0.82
RDW-CV (%)	67.0	59.0	51.0	57.86	0.99	1.71
WBC (x109/L)	16.5	13.5	10.5	13.10	0.21	1.60

NEU (x109/L)	19.90	17.40	14.90	17.99	0.45	2.50
NEU (%)	12.97	11.57	10.17	12.36	0.18	1.46
LYM (x109/L)	74.5	66.50	58.5	68.72	1.24	1.80
LYM (%)	4.53	3.13	1.73	3.38	0.11	3.25
MON (x109/L)	26.0	18.00	10.00	18.78	0.34	1.81
MON (%)	1.48	0.78	0.08	0.58	0.11	18.97
EOS (x109/L)	8.5	4.5	0.5	3.18	0.54	16.98
EOS (%)	3.30	1.91	0.52	1.69	0.16	9.47
BAS (x109/L)	19.0	11.0	3.0	9.33	0.70	7.50
BAS (%)	15.36	13.62	11.88	13.84	0.38	2.75
PLT (x109/L)	86.3	78.3	68.3	76.88	0.58	0.75
PCT (%)	514	454	394	445.6	12.9	2.89
PDW (%)	0.61	0.41	0.21	0.38	0.01	2.63
MPV (fL)	19.5	16.5	13.5	16.91	0.11	0.65
	11.9	8.9	5.9	8.46	0.08	0.95

Normality Statistics of Hematological Parameters of Pregnant Women of Taita-Taveta County, Kenya

The normality statistics for the levels of hematological parameters of pregnant women of Taita-Taveta County, Kenya were carried out to define the descriptive statistics to be used in expressing this dataset. Results of the twenty-three measured hematological parameters indicate that the data set of 22 parameters was not normally distributed except that of the mean platelet volume (MPV) (Table 2). Therefore this whole dataset was expressed as median and range; comparisons between the second and the third trimester were therefore statistically executed using Mann-Whitney U test.

Table 2: Results of the Normality Statistics of Hematological Parameters of Pregnant Women of Taita-Taveta County, Kenya

Parameter	Normality Statistics				
	Mean	Median	Mode	Skewness	Kurtosis
RBC (x1012/L)	4.06	4.00	4.00	-1.155	11.827
HB (g/dL)	11.16	11.10	11.00	-1.974	12.492
PCV (%)	1.85	0.33	0.00	6.579	45.627
MCH (pg)	28.07	28.20	29.00	6.093	77.133
MCHC (g/dL)	33.51	33.80	34.00	-3.684	25.668
MCV (fL)	81.51	82.90	86.80	-3.493	20.669
RDW-SD (%)	46.90	45.20	42.00	1.771	3.525
RDW-CV (%)	13.61	12.90	12.00	3.217	16.743
WBC (x109/L)	8.22	7.83	8.00	1.121	1.913
NEU (x109/L)	5.63	5.18	4.00	1.351	2.792
NEU (%)	65.77	67.20	66.00	-1.989	7.958
LYM (x109/L)	2.15	2.00	2.00	4.445	33.640
LYM (%)	26.68	25.90	28.00	0.899	3.138
MON (x109/L)	0.33	0.28	0.00	3.008	16.499
MON (%)	4.18	3.80	2.00	3.289	20.614
EOS (x109/L)	0.21	0.12	0.00	15.239	249.207
EOS (%)	2.18	1.80	2.00	5.102	46.767
BAS (x109/L)	0.032	0.030	0.030	6.698	70.128

BAS (%)	0.42	0.40	0.30	2.162	14.021
PLT (x109/L)	243.61	236.00	231.00	2.533	20.950
PCT (%)	0.20	0.20	0.00	6.124	75.030
PDW (%)	15.89	16.00	16.00	-6.189	46.975
MPV (fL)	9.01	9.00	9.00	0.392	-0.152

Established Trimester Specific Reference Intervals for Hematological Parameters for Pregnant Women of Taita Taveta County, Kenya

The established reference intervals for hematological parameters for pregnant women in their second and third trimester of Taita Taveta County, Kenya are reported in Table 3. Results indicate that, the established reference intervals for hematological parameters for the pregnant women of Taita-Taveta County, Kenya for RBC (x1012/L), HB (g/dL), MCH (pg), MCHC (g/dL), MCV (fL), RDW-CV (%), RDW-SD (%), WBC (x109/L), NEU (x109/L), NEU (%), LYM (x109/L), LYM (%), MON (x109/L), MON (%), BAS x109/L, EOS (x109/L), EOS (%), PLT (109/L), PCT (%), PDW (%) and MPV (fL) in their second trimester were similar to those of pregnant women in their third trimester ($\rho > 0.05$). Therefore trimester independent reference intervals of these parameters for this population were established. The established trimester independent reference interval for the pregnant women of Taita-Taveta County, Kenya for RBC is 4.0 (3.2-5.2) x1012/L, HB is 11.1 (7.8-14.3) g/dL, MCH is 28.2 (20.8-33.2) pg, MCHC is 33.8 (28-36.5) g/dL, MCV is 82.9 (61.9-94.8) fL, RDW-CV is 12.8 (11.3-20.85) %, RDW-SD is 45.1 (38-69.5) %, WBC is 7.8 (4.4-15.11) x109/L, NEU is 5.23 (2.3-12.5) x109/L, NEU is 67.4 (39.08-85.9) %, LYM is 2.04 (1.0-4.4) x109/L, LYM is 25.8 (10.8-44) %, MON is 0.3 (0.1-1.0) x109/L, MON is 3.8 (1.8-10.1) %, EOS is 0.14 (0.07-0.63) x109/L, EOS is 1.8 (0.3-6.21) %, BAS is 0.14 (0.1-0.6) x109/L, PLT is 237 (128-388.4) x109/L, PCT is 0.211 (0.2-0.3) %, PDW is 45.1 (38-69.5) %, and MPV is 8.9 (7.5-11) fL.

The established reference intervals for BAS (x109/L), BAS % and PVC (%) for pregnant women in their second trimester of Taita-Taveta County, Kenya significantly differed from those of pregnant women in their third trimester of the same County ($\rho < 0.05$). The established trimester dependent reference intervals for this population of Taita-Taveta County, Kenya for BAS is 0.03 (0.01-0.14) x109/L for pregnant women in their second trimester, and 0.03 (0-0.60) x109/L for pregnant women in their third trimester, BAS is 0.5 (0.2-0.99) % for pregnant women in their second trimester and 0.4 (0.1-0.90) % for pregnant women in their third trimester, and PCV is 0.3 (0.3-71.2) % for pregnant women in their second trimester and 0.3 (0.3-45) % for pregnant women in their third trimester (Table 3).

Table 3: Established trimester specific reference intervals for hematological parameters for pregnant women of Taita Taveta County, Kenya

Analyte (Unit)	Trimister	N	Median	Percentiles		Reference Interval	IV	Difference between M&F	
				2.5th	97.5th			Z value	Sig
RBC (x1012/L)	2&3	296	4.0	3.2	5.2	3.2-5.2	2	1.079	$\rho = 0.2805$
	2	124	4.2	3.2	5.2	3.2-5.2	2		
	3	172	4.0	3.2	5.3	3.2-5.3	2.1		
HB (g/dL)	2&3	296	11.1	7.8	14.3	7.8-14.3	6.5	0.730	$\rho = 0.466$
	2	124	11.2	7.9	14.3	7.9-14.3	6.4		
	3	172	11.1	7.7	14.5	7.7-14.5	6.8		
PCV (%)	2&3	296	0.3	0.3	34.4	0.3-34.4	34.1	2.305	$\rho = 0.021$
	2	124	0.3	0.3	71.2	0.3-71.2	70.9		
	3	172	0.3	0.3	45	0.3-45.0	44.7		
MCH (pg)	2&3	296	28.2	20.8	33.2	20.8-33.2	12.4	0.428	$\rho = 0.669$
	2	124	28.4	22.5	33.5	22.5-33.5	11		
	3	172	28.1	19.6	33.7	19.6-33.7	14.1		
MCHC (g/dL)	2&3	296	33.8	28	36.5	28-36.5	8.5	1.337	$\rho = 0.181$
	2	124	33.6	23	36.6	23-36.6	13.6		
	3	172	33.7	29.2	36.5	29.2-36.5	7.3		
MCV (fL)	2&3	296	82.9	61.9	94.8	61.9-94.8	32.9	0.643	$\rho = 0.52$
	2	124	82.7	29.5	94.8	29.5-94.8	65.3		
	3	172	82.9	61.5	93.4	61.5-93.4	31.9		
RDW-SD (%)	2&3	296	45.1	38	69.5	38-69.5	31.5	1.851	$\rho = 0.640$
	2	124	46	39.2	72.6	39.2-72.6	33.4		
	3	172	45.2	37.8	65.5	37.8-65.5	27.7		

RDW-CV (%)	2&3	296	12.8	11.27	20.85	11.3-20.9	9.6	1.104	ρ = 0.269
	2	124	13.1	11.12	23	11.1-23	11.9		
	3	172	12.8	11.33	20.3	11.3-20.3	9		
WBC (x109/L)	2&3	296	7.8	4.4	15.1	4.4-15.1	10.7	0.581	ρ = 0.56
	2	124	7.7	4.4	15.3	4.4-15.3	10.9		
	3	172	7.8	4.5	14.6	4.5-14.6	10.1		
NEU (x109/L)	2&3	296	5.2	2.3	12.5	2.3-12.5	10.2	0.644	ρ = 0.52
	2	124	5.0	2.3	13	2.3-13	10.7		
	3	172	5.4	2.3	12.71	2.3-12.7	10.4		
NEU (%)	2 & 3	296	67.4	39.1	85.9	39.1-85.9	46.8	1.277	ρ = 0.201
	2	124	66.8	11.5	85.9	11.5-85.9	74.4		
	3	172	68.1	44.7	85.8	44.7-85.8	41.1		
LYM (x109/L)	2&3	296	2.0	1.0	4.4	1-4.4	3.4	0.180	ρ = 0.857
	2	124	2.0	1.0	4.5	1-4.5	3.5		
	3	172	2.0	0.9	3.9	2-3.9	1.9		
LYM (%)	2 & 3	296	25.8	10.8	44	10.8-44	33.2	0.522	ρ = 0.602
	2	124	25.9	10.8	42.13	10.8-42.1	31.3		
	3	172	25.5	10.8	45	10.8-45	43.2		
MON (x109/L)	2&3	296	0.3	0.12	1.03	0.12-1.03	0.91	0.377	ρ = 0.880
	2	124	0.31	0.11	1.1	0.11-1.1	0.99		
	3	172	0.29	0.13	0.83	0.13-0.83	0.7		
MON (%)	2 & 3	296	3.8	1.8	10.05	1.8-10.05	8.25	0.147	ρ = 0.883
	2	124	3.6	1.81	10.41	1.81-10.41	8.6		
	3	172	3.8	1.83	9.34	1.83-9.34	7.51		
EOS (x109/L)	2&3	296	0.14	0.07	0.63	0.07-0.63	0.56	0.290	ρ = 0.770
	2	124	0.14	0.01	0.63	0.01-0.63	0.62		
	3	172	0.14	0.02	0.65	0.02-0.65	0.63		
EOS (%)	2&3	296	1.8	0.3	6.21	0.3-6.21	5.91	0.280	ρ = 0.88
	2	124	1.7	0.1	6	0.1-6	5.9		
	3	172	1.9	0.4	7.82	0.4-7.82	7.42		
BAS (x109/L)	2&3	296	0.03	0.01	0.08	0.01-0.08	0.07	2.966	ρ = 0.030
	2	124	0.03	0.01	0.14	0.01-0.14	0.13		
	3	172	0.03	0	0.6	0.00-0.6	0.6		
BAS (%)	2 & 3	296	0.4	0.1	0.94	0.1-0.94	0.84	2.676	ρ = 0.0075
	2	124	0.5	0.2	0.99	0.2-0.99	0.79		
	3	172	0.4	0.1	0.9	0.1-0.90	0.80		
PLT (x109/L)	2&3	296	237	128	388.4	128-388	260	1.646	ρ = 0.99
	2	124	228.5	103.1	387.9	103-388	285		
	3	172	239	128.3	396.8	128-397	269		
PCT (%)	2&3	296	0.21	0.12	0.34	0.12-0.34	0.22	1.403	ρ = 0.161
	2	124	0.2	0.10	0.33	0.10-0.33	0.23		
	3	172	0.21	0.12	0.35	0.12-0.35	0.23		
PDW (%)	2&3	296	45.1	38	69.5	38-69.5	31.5	3.145	ρ = 0.64
	2	124	46	39.2	72.6	39.2-72.6	33.4		
	3	172	45.2	37.8	65.6	37.8-65.6	27.8		

MPV (fL)	2&3	296	8.9	7.5	11	7.5-11	3.5	0.918	$\rho = 0.354$
	2	124	8.9	7.5	11.4	7.5-11.4	3.9		
	3	172	8.9	7.1	11	7.1-11	3.9		

Results are expressed as Median and range for the number of referent participants in the column labeled N. Statistical comparisons of the median values between the second and third trimester was carried out using Mann-Whitney U test. Differences were considered statistically significant at $\rho < 0.05$.

Comparison of Developed Trimester Specific Reference Intervals of Hematological Parameters for Pregnant Women of Taita-Taveta County, Kenya with those Reported in Literature

A comparison of developed reference intervals for hematological parameters for pregnant women in their second and third trimester of Taita-Taveta County, Kenya population with those reported in medical literature are presented in Table 4. Results indicate that, this study's trimester independent lower reference interval limits for RBC (x1012/L) for pregnant women in their second and third trimester is similar to that of the north-western Moroccan population, higher than that of the western Kenya and African women populations, but lower than that of western Indian, north west Ethiopia, and Australianpopulations [2,5,6,7,10,11,]. The upper limit is higher than that of the northwestern Moroccans, western Kenya, North West Ethiopia, and Australian populations, lower than that of the western Indian, and lower and similar to that of African women population [2,5,6,7,10,11].

This study's trimester independent lower reference interval limits for HB (g/dL) for pregnant women in their second and third trimester is similar to that of the western Indian population, lower than that of the northwestern Moroccan, African women, and Australian and lower and similar to that of north West Ethiopia populations, and higher than that of the western Kenya, and Lagos Nigerian population [2,3,5,6,7,10,11]. The upper limit was higher than that of the western Indian, North West Ethiopia, African Women, western Kenya, northwestern Moroccan, and Australian, and similar and higher to that of Lagos Nigerian populations [2,3,5,6,7,10,11].

This study's trimester dependent lower reference interval limit for PCV (%) for pregnant women in their second and third trimester is lower than that of western Kenya, western Indian, northwestern Moroccan, and Australian populations, while the upper limit is higher than that of western Kenya, western Indian, Australian, and northwestern Moroccan populations [2,5,6,7].

This study's trimester dependent lower reference interval limit for MCH (pg) for pregnant women in their second and third trimester is similar to that of western Indian population, lower than that of Lagos Nigerian, North West Ethiopia, western Kenya, north-western Moroccan, Australian populations. The upper limit is similar to that of the north-western Moroccan, western Indian and Australian populations, but lower than that of the North West Ethiopia, western Kenya, and lower and higher to that of Lagos Nigerian population [2,3,5,6,7,11].

For MCHC (g/dL), this study's lower reference interval limit for pregnant women in their second and third trimester is lower than that of the Lagos Nigerian, north-western Moroccan and Australian populations, but higher than that of African women, and western Indian population [2,3,6,7,10]. The upper limit is similar to that of the north-western Moroccan, and Australian populations, but lower than that of the western Indian, and African women, and similar and higher than that of Lagos Nigerian population [2,3,6,7,10].

For MCV (fL), this study's trimester independent lower reference interval limit for pregnant women in their second and third trimester is lower than that of the western Indian, North West Ethiopia, north-western Moroccan, and Australian, and lower and higher than that of Lagos Nigerian populations [2,3,6,7,11]. The upper limit is lower than that of Australian women, North West Moroccan women, western India women, and western Kenya women, higher than that of Lagos Nigerians, and similar to that of North West Ethiopian populations [2,3,5,6,7,11].

For RDW-CV (%), this study's trimester independent lower reference interval limit for pregnant women in their second and third trimester is higher and similar, respectively, to that of the western Indian population, while the upper limit is similar and higher, respectively, to this same Indian population [6].

Further, for WBC and differential white blood cells, this study's trimester independent lower reference interval limit for WBC (x109/L) for pregnant women in their second and third trimester is lower than that of the Israel women, north west Ethiopia, north-western Moroccan, western Indian, and Australian populations, but higher than that of the African women, Lagos Nigerian, and western Kenya population [2,3,5,6,7,10,11,12]. The upper limit is higher than that of the Lagos Nigerian, Israel women, African women, north west Ethiopians, north-western Morocco, western Kenya, and western Indian populations; however, for the Australian population, this study's upper limit for WBC (x109/L) for pregnant women in their second trimester is lower while that in the third trimester is higher [2,3,5,6,7,10,11,12].

For NEU (x109/L), this study's trimester independent lower reference interval limit for pregnant women is similar to north-western Moroccans in their second trimester, but lower than that of the Israel, north-western Moroccans in their third trimester, higher than that of western Kenya, and lower than that of Australian population [2,5,7,12]. The upper limit is higher than that of Israel, north-western Morocco, and western Kenya populations, but similar to that of Australians in their second trimester and lower than that of Australians in their third trimester. For NEU (%), this study's trimester independent lower reference interval limit for pregnant women in their second and third trimester is lower than that of Israel and west India populations, while the upper limit higher than that of Israel and lower than that of west India populations [2,5,6,7,12].

For LYM (x109/L), this study's lower reference interval limit for pregnant women in their second and third trimester is similar to that of Israel, north-western Morocco, western Kenya, and Australian populations [2,5,7,12]. The upper limit is higher than that of Israel, north-western Morocco, western Kenya, and Australian populations [2,5,7,12]. For LYM (%), this study's trimester independent lower reference interval limit for pregnant women in their second and third trimester is higher than that of west India, and lower than that of Israel and African populations, while the upper limit higher than that of Israel, and west India, and lower than that of African women populations [6,10,12,].

For MON (x109/L), this study's trimester independent lower reference interval limit for pregnant women is lower than that of African , lower and similar to that of Israel, similar to that of north-western Moroccan, western Kenya, and Australian population [2,5,7,10,12]. The upper limit is similar to that of north-western Moroccan, higher than that of western Kenya,

and lower than that of the African, Israel, and Australian population. For MON (%), this study's trimester independent lower reference interval limit in their second and third trimester is lower than that of Israel, and higher than that of west India population, while the upper limit is higher than that of Israel, and west India population [2,5,6,7,10,12].

For EOS (x109/L), this study's trimester independent lower reference interval limit for pregnant women is higher than that of Israel, north-western Moroccan, western Kenya, and Australian populations, while the upper limit is similar to that of the Australian, higher than that of north-western Morocco, and lower than that of Israel, and western Kenya population. For EOS (%), this study's lower reference interval limit for pregnant women in their second and third trimester is higher than that of the Israel , and lower than that of west India population, while the upper limit is higher than that of Israel , and higher and similar to that of west India population [2,5,6,7,12].

For BAS (x109/L), this study's trimester dependent lower reference interval limit for pregnant women is higher than that of (trimester independent) Israel, similar to that of north-western Morocco and Australian populations [2,7,12]. The upper limit is higher than that of Israel, north-western Moroccans and Australians. For BAS (%), this study's trimester dependent lower and upper reference interval limit for pregnant women in their second and third trimester are higher than that of the trimester independent Israel population [2,12].

In addition, for PLT (x109/L), this study's trimester independent lower reference interval limit for pregnant women is higher than that of western Kenya, [Lagos Nigerian, African women], but lower than that of north-western Morocco, Australian, [north west Ethiopia] and western Indian populations [5,3,10,2,7,11]. The upper limit is lower than that of western Kenya, and Australian populations, similar and higher for western India, and higher than that of Lagos Nigerians, north west Ethiopians, and African women populations in their second and third trimester, respectively [3,5,6,7,10,11]. For MPV (fL), this study's trimester independent lower and upper reference interval limits for pregnant mothers is lower than that of the north-western Moroccans [2].

Table 4: Comparison of developed trimester specific reference intervals of hematological parameters for pregnant women of Taita-Taveta County, Kenya with those reported in literature

Analyte (unit)	Trimister	This study RI	Northwest Morocco	Western Kenya	Western India	Australian population	Lagos Nigerians	North-western Ethiopians	African women	Israel women
RBC (x1012/L)	2&3	3.2-5.2						4.30-4.44		
	2	3.2-5.2	3.26-4.82	2.8-4.8	3.6-4.5	3.43-4.49*			2.65-4.92*	
	3	3.2-5.3	3.19-4.78	2.8-4.9	0.6-7.7	3.38-4.43			2.87-5.34	
HB (g/dL)	2&3	7.8-14.3						12.99-13.36		
	2	7.9-14.3	9.6-13.6	6.1-13.0*	8.0-12.1	10.6-13.3	7.44-14.18*		8.2-13.2*	
	3	7.7-14.5	9.1-13.4	5.5-12.7	7.6-12.5	10.4-13.5	7.89-12.87		9.0-13.95	
PCV (%)	2 &3	0.3-34.4								
	2	0.3-71.2*	28.6-39.9*	21.4-38.1*	27.1-38.7	31-39	19.55-39.97*	39.63-41.14*	23.8-39.4*	
	3	0.3-45	27.3-39.3	17.7-38.6	27.3-40.1	31-40	25.44-40.64	41.17-42.75	25.9-41.85	
MCH (pg)	2&3	20.8-33.2						28.88-34.81		
	2	22.5-33.5	24.0-33.3		20.5-33.5	27-33	23.73-33.53			
	3	19.6-33.7	23.0-33.4		22.4-32.3	28-33	24.42-31.94			
MCHC (g/dL)	2&3	28-36.5						31.91-33.37		
	2	23-36.6	31.2-36.6		29.1-36.9	33-36	34.37-38.61*			
	3	29.2-36.5	30.8-36.2		17.4-43.5	33-36	29.87-32.81			

MCV (fL)	2&3	61.9-94.8						93.33-94.63		
	2	29.5-94.8	74.7-97.7	58-101	66.5-99.3	83-96	67.17-89.59*			
	3	61.5-93.4	72.8-96.1	59-99	58.5-112.9	85-97	59.44-80.60			
RDW-CV (%)	2&3	11.3-20.9								
	2	11.1-23			10.3-19.8*					
	3	11.3-20.3			11.4-26.5					
RDW-SD (%)	2&3	38-69.5								
	2	39.2-72.6								
	3	37.8-65.5								
WBC (x109/L)	2&3	4.4-15.1						8.60-9.61		
	2	4.4-15.3	4.6-12.6*	3.6-11.1*	4.9-14.5*	6.2-14.8*	3.33-12.43*		3.3-11.1	5.22-12.20*
	3	4.5-14.6	5.3-14.3	3.3-10.7	6.0-14.3	5.9-16.9	4.10-12.52		3.8-11.2	5.12-13.20
NEU (x109/L)	2&3	2.3-12.5								
	2	2.3-13	2.2-9.2*	1.9-7.1*		3.8-12.3*				3.37-9.05*
	3	2.3-12.7	3.0-11.0	2.0-5.7		3.9-13.1				3.26-9.76
NEU (%)	2&3	39.1-85.9								
	2	11.5-85.9			59.6-87.9					62.9-79.5
	3	44.7-85.8			52.9-88.4					61.7-79.7
LYM (x109/L)	2&3	1-4.4						2.11-2.33		
	2	1-4.5	1.2-3.6*	0.9-3.3*		0.9-3.9*				0.85-2.69*
	3	2-3.9	1.1-3.8	1.2-3.8		1.0-3.6				1.01-2.75
LYM (%)	2&3	10.8-44								
	2	10.8-42.1			8.1-31.2				19-57	11.2-30.8
	3	10.8-45			6.5-33.2				18.1-53.6	12.5-30.1
MON (x109/L)	2&3	0.12-1.03								
	2	0.11-1.1	0.2-1.0	0.1-0.9		0.1-1.1*			1.7-17*	0.163-0.705*
	3	0.13-0.83	0.1-1.0	0.1-0.8		0.1-1.4			1.1-23.1	0.120-0.874
MON (%)	2&3	1.8-10.05								
	2	1.81-10.41			1.8-5.0					2.2-7.8
	3	1.83-9.34			1.2-5.6					2-9
EOS (x109/L)	2&3	0.07-0.63								0-0.326
	2	0.01-0.63	0-0.4	0-0.9		0-0.6				
	3	0.02-0.65	0-0.4	0-1.0		0-0.6				
EOS (%)	2&3	0.3-6.21								0-3.9
	2	0.1-6			1.4-5.8					
	3	0.4-7.82			0.9-6.3					
BAS (x109/L)	2&3	0.01-0.08								
	2	0.01-0.14*	0-0.1	0.01-0.12*		0-0.1				0.003-0.067
	3	0-0.60	0-0.1	0.01-0.09		0-0.1				0.006-0.068

BAS (%)	2&3	0.1-0.94								
	2	0.2-0.99*								0.04-0.80
	3	0.1-0.90								0.07-0.77
PLT (x109/L)	2&3	128-388						221-240		
	2	103-388	140-364*	98-395*	234-390*	171-409*	104-351*		97-350*	
	3	128-397	139-398	105-425	170-338	155-429	15.8-385.8		86.5-344.5	
PCT (%)	2&3	0.12-0.34								
	2	0.10-0.33								
	3	0.12-0.35								
PDW (%)	2&3	38-69.5								
	2	39.2-72.6								
	3	37.8-65.6								
MPV (fL)	2&3	7.5-11								
	2	7.5-11.4	8.9-13.5							
	3	7.1-11	8.9-13.2							

Australian population by Balloch and Cauchi (1993), Israel population by Lurie et al. (2008), African women (Malawians, Tanzanians & Zambians) population by Mwinga et al. (2009), Lagos Nigerians by Akinbami et al. (2013), Western India population by Purohit et al. (2015), Northwest Ethiopians by Genetu et al. (2017), Western Kenya population by Odhiambo et al. (2017), and Northwest Morocco population by Bakrim et al. (2018). Italicized values represent trimester independent reference intervals; stared* values represent trimester dependent reference intervals.

Discussion

Results of this study indicating statistically nonsignificant difference in the reference intervals for red blood cells (RBC) (3.2-5.2 x1012/L), hemoglobin (HB) (7.8-14.3 g/dL), mean cell hemoglobin (MCH) (20.8-33.2 pg), mean cell hemoglobin concentration (MCHC) (28.0-36.5 g/dL), mean cell volume (MCV) (61.9-94.8 fL), red blood cell distribution width (RDW-CV) (11.27-20.85 %), red blood cell distribution width (RDW-SD) (38.0-69.5 %), white blood cells (WBC) (4.4-15.1 x109/L), lymphocytes (LYM) (1.0-4.4 x109/L; 10.8-44.0 %), neutrophils (NEU) (2.3-12.5 x109/L; 39.1-85.9 %), eosinophils (EOS) (0.07-0.63 x109/L; 0.30-6.21 %), monocytes (MON) (0.12-1.03 x109/L; 1.8-10.1 %), platelets (PLT) (128-388.4 x109/L), platelet crit (PCT) (0.12-0.34 %), platelet distribution width (PDW) (38.0-69.5 %), and mean platelet volume (MPV) (7.5-11.0 fL) in pregnant women in the second trimester compared to the third trimester imply that there are no trimester related alterations in these hematological parameters for this population in this environment. These results contrast the expected decrease in RBC, HB, and PLT due to increase in plasma volume which occurs faster than the increase in erythrocyte mass secondary to sodium and water reabsorption leading to hemodilution and the increased need for minerals and vitamins (iron, vitamin B12, folic acid) for fetal hematopoiesis. This is transmitted via renin-angiotensin-aldosterone pathway activation by increased secretion of progesterone and estrogen by the placenta during pregnancy. This is the modification of the physiology of a pregnant woman that occurs in order to compensate for the needs brought about by the fetus and its environment [4]. The non-significant changes in the hematological parameters observed in this study could be explained by a fast hemodilution in the first trimester which seems to level off in the second and third trimester as demonstrated in the reduced changes in the hematological parameters as reported by Bakrim et al. (2018), Odhiambo et al. (2017), Purohit et al. (2015), and Balloch and Cauchi (1993). Alternatively, it could be that pregnant women on minerals and vitamins (iron, vitamin B12, folic acid) and antimalarial supplementation as occurs in this population for this County and the rest of Kenyan Counties have less pronounced hematological changes because their increase in red blood cell mass is proportional when compared to pregnant women not on minerals and vitamins (iron, vitamin B12, folic acid) and antimalarial supplementation [6,11]. In agreement with the current study, Balloch and Cauchi (1993) reported trimester independent reference intervals for HB, MCH, MCHC, MCV, MON, and EOS, Lurie et al. (2008) reported trimester independent reference intervals for EOS and BAS, Mwinga et al. (2009) reported trimester independent reference intervals for WBC and LYM (%), Purohit et al. (2015) reported trimester independent reference intervals for RBC, HB, MCH, MCHC, MCV, NEU, LYM, MON and EOS, Odhiambo et al. (2017) reported trimester independent reference intervals for RBC, MCV, MON and EOS, Genetu et al. (2017) reported trimester independent reference intervals for RBC, HB, MCH, MCHC, MCV, WBC, LYM and PLT, and Bakrim et al. (2018) reported trimester independent reference intervals for RBC, HB, MCH, MCHC, MCV, MPV, MON, BAS, and EOS for pregnant women in their second and third trimester. In contrast to the current study, Balloch and Cauchi (1993) reported trimester dependent decrease in the reference interval for RBC (3.43-4.49 g/dL versus 3.38-4.43 g/dL), and LYM (0.9-3.9 x109/L versus 1.0-3.6 x109/L), and an increase in the reference interval for WBC (6.6-14.8 x109/L versus 5.9-16.9 x109/L), NEU (3.8-12.3 x109/L versus 3.9-13.1 x109/L), MON (0.1-1.1 x109/L versus 0.1-1.4 x109/L), and PLT (171-409 x109/L versus 155-429 x109/L); Lurie et al. (2008) reported trimester dependent increase in the reference intervals for WBC (5.22-12.20 x109/L versus 5.12-13.20 x109/L), NEU (3.37-9.05 x109/L versus 3.26-9.76 x109/L), LYM (0.85-2.69 x109/L versus 1.01-2.75 x109/L), and MON (0.163-0.705 x109/L versus 0.120-0.874 x109/L); Mwinga et al. (2009) reported a trimester dependent increase in the reference intervals for RBC (2.65-4.92 x1012/L versus 2.87-5.34 x1012/L), HB (8.2-13.2 g/dL versus 9.0-13.95 g/dL) and MON (1.7-17 % versus 1.1-23.1 %), and a decrease in PLT (97-350 x109/L versus 86.5-344.5 x109/L); Akinbami et al. (2013) reported trimester dependent decrease in reference intervals for HB (7.44-14.18 versus 7.89-12.87 g/dL), MCHC (34.37-38.61 g/dL versus 29.87-32.81 g/dL), MCV (67.17-89.57 fL versus 59.44-80.60 fL), PLT (104.09-351.05 x109/L versus 15.80-385.84 x109/L), and an increase in WBC (3.33-12.43 x1012/L versus 4.10-12.52 x1012/L); Purohit et al. (2015) reported trimester dependent increase in RDW-CV (10.3-19.8 % versus 11.4-26.5 %) and WBC (4.9-14.5 x109/L versus 6.0-14.3 x109/L) and a decrease in PLT (234-390 x109/L versus 170-338 x109/L); Odhiambo et al. (2017) reported trimester dependent reference intervals decrease in HB (6.1-13.0 g/dL versus 5.5-12.7 g/dL), WBC (3.6-11.1 x 109/L versus 3.3-10.7 x 109/L), and BAS (0.01-0.12 x 109/L ver-

sus 0.01-0.09 x 109/L), and increase in PLT (98-395 x 109/L versus 105-425 x 109/L), NEU (1.9-7.1 x 109/L versus 2.0-5.7 x109/L), and LYM (0.9-3.3 x 109/L 4versus 1.2-3.8 x 109/L); and Bakrim et al. (2018) also reported trimester dependent increase in WBC (4.6-12.6 x 109/L versus 5.3-14.3 x 109/L), NEU (2.2-9.2 x 109/L versus 3.0-11.0 x109/L), LYM (1.2-3.6 x 109/L versus 1.1-3.8 x 109/L), and PLT (140-364 x 109/L versus 139-398 x 109/L) from the second to the third trimester. These differences highlight the need for the use of locally developed reference intervals for clinical management of pregnancy related disease conditions in pregnant women.

Results of this study indicating that the reference interval of the packed cell volume (PCV) (0.3-71.2 %), and basophils (BAS) (0.01-0.14 x109/L) of pregnant women of Taita-Taveta County population in their second trimester is significantly higher, and lower than that of their counter parts in the third trimester (0.3-45.0 %) and (0.0-0.60 x109/L), respectively, implies that these hematological parameters are trimester dependent for this referent population. The significant decrease in the reference intervals for PCV in the third trimester of pregnant women of Taita-Taveta County population compared to those in the second trimester of the same county could be due to decreased red blood cells (RBC) explained by hemodilution resulting from the increase in plasma volume. The increase in progesterone and estrogen secreted from the placenta during pregnancy induces release of renin from the kidneys and reduces the release of atrial natriuretic peptide from the heart. Renin stimulates the conversion of angiotensinogen released from the liver to angiotensin I which in turn is converted to angiotensin II by angiotensin converting enzyme (ACE) released from the endothelial cells of the lungs. Angiotensin II acts directly on blood vessels to induce vasoconstriction, and on the adrenal cortex to stimulate the production of aldosterone which in turn acts on the kidneys to promote sodium and water reabsorption which increase the plasma volume (blood volume). The increase in blood volume and induction of vasoconstriction induce an increase in blood pressure. The increase in plasma volume (40 %) is more pronounced than the increase in red blood cell mass (20 %) and therefore leading to a decrease in maternal hemoglobin concentration causing physiological anemia [6,13]. It may not be associated with malaria infection since all pregnant women in Taita-Taveta County were on antimalarial drugs (Fansidar) as a prophylactic measure after sixteen weeks of pregnancy when the fetal heart beat is noticeable. The significant increase in the reference intervals for BAS in the third trimester of pregnant women of Taita-Taveta County population relative to those in the second trimester of the same county could be explained by the increased production of basophil granule major basic protein (MBP) [14]. The pregnancy associated major basic protein (MBP) localized in placental X cells and placental-site giant cells is indistinguishable from basophil granule major basic protein (MBP) immunochemically and biochemically: they have the same molecular weight, isoelectric point, and the same peptide map. Basophil granule major basic protein (MBP) is associated with alteration of tracheal smooth muscle contractility. Together with alteration of the levels of histamine, estrogen, progesterone, prostaglandins, and oxytocin in complex interaction, basophil MBP could also be associated with induction of labor by altering myometrial smooth muscle contractility and cervical ripening [14]. Its supply is ensured by the elevated levels of basophils during the third trimester of pregnancy. The observed decrease in PCV (0.3-71.2 % versus 0.3-45 %) in this study from the second to the third trimester is in agreement with the decrease reported by Odhiambo et al. (2017) (21.4-38.1 % versus 17.7-38.6 %) for western Kenyans. However, it contrasts the increase (23.8-39.3 % versus 25.5-41.85 %) reported by Mwinga et al. (2009), Akinbami et al. (2013) (19.55-39.97 % versus 25.44-40.64 %), Purohit et al. (2015) (27.1-38.7 % versus 27.3-40.1 %), and Genetu et al. (2017) (39.63-41.44 % versus 41.17-42.75 %) even though the study subjects were on iron supplementation. The observed increase in BAS (0.01-0.14 x109/L versus 0.0-0.60 x109/L) in this study from the second to the third trimester contrasts the decrease (0.01-0.12 x109/L versus 0.01-0.09 x109/L) reported by Odhiambo et al. (2017) and the non-significant alteration reported by Lurie et al. (2008) and Balloch and Cauchi (1993).

One limitation of this study was that it did not include a sample from non-pregnant women from the same referent population to generate baseline data. Another limitation was that it was not possible to recruit pregnant women early enough so as to capture enough of them while in their first trimester. Other limitations included the variation in the number of pregnant women in each trimester due to exclusion of participants during screening, and the time for drawing blood varied daily which may have increased the reference intervals due to the circadian rhythms. Further, this study neither screened and removed iron deficient referent subjects nor identify and remove referent subjects with hemoglobin related diseases. However, the pregnant referent population were supplemented with mineral, vitamins and antimalarial drugs (Fansidar) immediately after the confirmation of the fetal heat beat and were therefore not expected to suffer from mineral and vitamin deficiency related diseases and malarial infection. This, however, required confirmation by measuring the levels of iron, transferrin, and iron binding capacity, which was not done.

In conclusion, this study developed the first trimester specific reference intervals for hematological parameters for healthy pregnant women living in Taita-Taveta County, Kenya which differs from those reported in medical literature. This difference of the developed reference intervals for pregnant women of Taita-Taveta County from those reported in literature supports the need for use of locally developed reference intervals for managing pregnancy related challenges for the pregnant women of Taita-Taveta County, Kenya. This pregnancy induced physiological changes of hematological parameters reference intervals require consideration during the assessment of the health status of normal pregnancy and for diagnosing conditions or challenges occurring during pregnancy for optimal maternal and fetal medical care. In addition, these developed reference intervals for pregnant women can also be adopted and used by researchers in this specific area [15].

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