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Total alkaline phosphatase levels by gestational age in a large sample of pregnant women

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Abstract

Introduction:

Total alkaline phosphatase (tALP) levels rise physiologically in maternal serum during pregnancy, and excessively so in certain conditions. However, current reference values are dated, nonlinear, and based on small samples. Factors related to variation in tALP remain unexplained. Thus, our goals in this study were to establish a physiological development curve for tALP within low-risk pregnancies and to evaluate the factors influencing tALP values.

Methods:

This was a single-center, retrospective, observational study. All patients who delivered a live singleton infant at our center from January 1, 2011 to May 31, 2019, and had a tALP assay during pregnancy, were included regardless of the gestational age at which the assay was conducted.

Results

A total of 2415 pregnancies were included. Median tALP decreased during the first trimester, it increased slightly during the second trimester, and then increased sharply during the third trimester. Factors associated with a significant increase in tALP were chronic histiocytic intervillitis, cholestasis, multiple pregnancies, liver disease, preeclampsia, smoking, and low weight for gestational age. Conversely, gestational diabetes was associated with a discrete decrease in tALP.

Discussion

Our large sample allowed establishment of tALP reference curves based on gestational age. To interpret these results more thoroughly, factors that influence tALP rates should be further scrutinized.

Keywords: alkaline phosphatase, pregnancy, smoothed curves

1 **1. Introduction**

2 Alkaline phosphatases (ALP) are ubiquitous enzymes that may originate in the liver,
3 bone, intestine, kidney, germ, or placenta [1]. During pregnancy, high total ALP
4 (tALP) levels are often associated with unfavorable obstetric prognosis [2–4],
5 although this association is debated regarding both preeclampsia [5–12] and small
6 for gestational age (SGA) neonates [2,13,14]. Recently, an association was shown
7 between elevated tALP and chronic histiocytic intervillitis, a rare and severe
8 disease of the placenta that is responsible for miscarriage, severe intrauterine growth
9 restriction, and in utero death [15].

10 Although the search for abnormal variations in tALP during pregnancy has been the
11 subject of much research, it is accompanied by several challenges. First, tALP rises
12 physiologically during pregnancy, primarily due to increases in placental and bone
13 isoenzymes [16], which means that gestational age must be accounted for as
14 accurately as possible when analyzing changes in tALP levels. Second, no high-
15 quality tALP curves are available throughout pregnancy; most current reference
16 values are dated, derived from small samples, and often reflect only one or two
17 values per trimester [16–24]. Moreover, large differences exist between published
18 values—as high as three times the median or mean—making interpretation difficult
19 [16,19,22,24].

20 Accordingly, our goals in this study were to establish a reference curve reflecting the
21 natural course of tALP throughout pregnancy from a large sample of low-risk
22 pregnancies, and to study the factors that influence these values.

23

24

25 **2. Materials and methods**

26 This was a single-center, observational, retrospective cohort study conducted at our
27 Level III university maternity hospital over eight consecutive years (January 1, 2011–
28 May 31, 2019). Pregnancies were eligible if their ICD-10 (10th International
29 Classification Diseases) codes indicated a single, live birth after at least 22 weeks of
30 gestation (WG), and if they had at least one tALP assay performed during pregnancy,
31 regardless of the gestational age at which it was performed. To eliminate situations
32 that may cause variations in tALP [2,5–10,13,25,26], pregnancies were excluded if
33 their ICD-10 codes indicated one or more of the following: preeclampsia, intrauterine
34 growth restriction, cholestasis, another liver disease, gestational or prepregnancy
35 diabetes, chronic histiocytic intervillitis, in utero death or medical termination of
36 pregnancy, alcoholism, or bone disease.

37 The study sample was selected from our center's medical and care information
38 system database (Sillage[®], SIB, Rennes, France) and biological data server (Molis[®],
39 CGM, Brussels, Belgium). These data were cross-referenced to PMSI-ICD10
40 database codings. The medical information collected included maternal
41 characteristics, gravida, prepregnancy medical history (e.g., diabetes, hypertension),
42 pregnancy-related history (e.g., hospitalization), gestational age at current delivery,
43 delivery mode, and neonatal birth weight. Our center routinely collects patient
44 consent for the anonymous use of the data in their medical records for clinical
45 research, which is administered through a routine document signed at admission to
46 the maternity ward. Our study was approved by our national ethics committee

47 (Comité d’Ethique de la Recherche en Obstétrique et Gynécologie, CEROG n°2019-
48 OBST-0703).

49 If a patient had more than one pregnancy during the study period, each pregnancy
50 was included and analyzed individually according to the inclusion and exclusion
51 criteria above. When several tALP assays were available for the same pregnancy,
52 only the first was retained and analyzed. All tALP determinations were performed
53 using the International Federation of Clinical Chemistry (IFCC) reference technique
54 [27], using the colorimetric method with spectrophotometric measurement of *p*-
55 nitrophenyl phosphate hydrolysis at 450/480 nm ; the same machine was used
56 during the whole study period (COBAS 8000 system, Roche Diagnostics, Meylan,
57 France).

58 Categorical variables are described as values and percentages, and quantitative
59 variables as medians and interquartile values [IQ25; IQ75]. At each gestational age,
60 tALP reference intervals were constructed using the parametric smoothing method of
61 Royston and Wright [28] to obtain the smoothed 2.5th, 10th, 50th, 90th, and 97.5th
62 percentiles. Each tALP value is also expressed as a multiple of the median (MoM) by
63 relating it to its median for gestational age. Median tALP values among excluded
64 patients were compared with reference values from the included sample. Then, the
65 influence of smoking and history of chronic hypertension were investigated in the
66 included sample.

67 Data were analyzed using Epi-info (Epi-info version 7.1.5, CDC, Atlanta, USA), SAS
68 version 9.4 (SAS Institute, Cary, USA), and R Core Team version 2019 (R Core
69 Team, Vienna, Austria). All median comparisons used the nonparametric Kruskal–
70 Wallis test. Significance levels for all tests were set at 5%.

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72

73 **3. Results**

74 Among the 66,136 pregnancies lasting at least 22 weeks in our center during the
75 study period, 6825 had at least one tALP assay (10.3%) (Fig. 1). According to our
76 criteria, we excluded those with gestational and prepregnancy diabetes (n=3209),
77 preeclampsia (n=813), intrauterine growth restriction (n=707), multiple pregnancy
78 (n=358), cholestasis (n=328), in utero death or medical termination (n=120), other
79 liver pathologies (n=38), chronic histiocytic intervillitis (n=28), alcoholism (n=3) and
80 bone pathologies (n=1). As some women had more than one exclusion criteria, a
81 final sample of 2415 pregnancies was included, with a single tALP measurement for
82 each. The number of women with an available assay ranged from 30 to 118 for each
83 gestational age between 2 and 41 SA, with a median of 48 assays per week of
84 gestation IQR 25-75 [41; 84].

85 The sample characteristics are presented in Table 1. The median maternal age was
86 30 years and 12.8% of pregnant women smoked; 42% were primigravida and 2.1%
87 had prepregnancy hypertension. The cesarean delivery rate was 21.5%; 8.6% were
88 premature deliveries and 7.6% of neonates were macrosomic (birth weight >4000 g).

89 The distribution of 2415 tALP values as a function of gestational age is shown in Fig.
90 2, with curves for the 2.5th, 10th, 50th, 90th, and 97.5th percentiles after Royston
91 and Wright parametric smoothing. After a slight decrease between gestational weeks
92 2–13 (first trimester), these values increased slightly in weeks 14–28 (second
93 trimester), and then increased sharply in weeks 29–41 (third trimester). Smoothed
94 tALP distribution values at each gestational age are shown in Table 2.

95 Median tALP values were 0.96 [0.79; 1.24] for the 2415 included pregnancies (Table
96 3). Factors associated with significantly higher median tALP values, in descending
97 order of MoM values [with 1st and 3rd interquartile ranges], were chronic histiocytic
98 intervillitis (1.61 [1.22; 2.86]), cholestasis (1.43 [1.04; 1.90]), multiple pregnancy
99 (1.32 [0.96; 1.79]), another liver disease (1.31 [1.00; 2.06]), preeclampsia (1.12 [0.88;
100 1.51]), smoking during pregnancy (1.10 [0.86; 1.45]), and SGA (1.08 [0.88; 1.51]).
101 Conversely, the occurrence of gestational diabetes was associated with slightly but
102 significantly lower tALP values (0.95 [0.78; 1.18]). Compared with the included
103 sample, tALP values did not differ significantly among excluded pregnancies with
104 prepregnancy diabetes, preexisting hypertension, or in utero death or medical
105 termination of pregnancy.

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107

108 **4. Discussion**

109 We plotted reference tALP values for a large sample of low-risk singleton
110 pregnancies. Several factors were significantly associated with an increased tALP
111 value (chronic histiocytic intervillitis, multiple pregnancy, cholestasis and other liver
112 diseases, preeclampsia, smoking, and SGA), whereas the presence of gestational
113 diabetes was associated with a slightly decreased tALP value.

114 Our tALP curve is derived from one of the largest cohorts to date. Only one cohort
115 was larger than ours, consisting of 13 656 Chinese women with measurements
116 whose medians and distribution are given solely for sequential periods of 6 or 7
117 consecutive weeks of pregnancy. For the others, previous reference values were
118 based on much smaller numbers, ranging from 30 to 103 women, with 3–7 tALP
119 measurements per patient [16,18–20,22,23,29], and two previous studies were meta-
120 analyses [17,21]. While tALP values rise in late pregnancy, none of the previous
121 curves provided smoothed reference values corresponding to each gestational week.
122 At best, they provided one or two reference values per trimester, and some curves
123 had no values available for an entire trimester [16,23]. In contrast, we have
124 established a curve informed by more than 2000 pregnancies, with a reference
125 median for each gestational age, allowing us to avoid variation in tALP values
126 according to pregnancy progression. Further, tALP determinations were performed
127 using the same process throughout the study period (i.e., with the IFCC reference
128 technique) [27].

129 It is difficult to compare our curves with those previously published. Some
130 publications report the median [23,24], others the mean [16,19,20,22], and still others

131 the 2.5th and 97.5th percentiles for gestational periods that differ slightly between
132 curves [17–19,21]. One curve—representing 103 women and published in 1996—is
133 distinguished by particularly low tALP values [22], while another—carried out in 30
134 women and published in 2006—is distinguished by average values that well exceed
135 the others for all trimesters [19]. Thus, certain medians or averages previously
136 reported may vary by two to three times [19,22]. Nevertheless, the values presented
137 herein are similar to most of those previously published, with a clearly demarked rise
138 beginning in the third trimester [16–18,20,21,23,24].

139 In addition to providing reference values based on a large volume of assays, our
140 curve allows us to clarify several points concerning changes in tALP across
141 pregnancy, and to explore these sources of variation. An important implication of
142 these findings concerns the decrease in tALP during the first trimester, that is, before
143 the well-known phases of slight and then strong increases in tALP during the second
144 and third trimesters, respectively [16,24]. We suggest that the tALP decrease in early
145 pregnancy is related to two well known factors, namely hemodilution and increased
146 glomerular filtration, which occur very early in pregnancy [30,31], and the « late »
147 production of specific placental alkaline phosphatases, which does not really begin
148 until the second trimester of pregnancy, when a rise in tALP is perceptible [16,24].
149 This production of placental isoenzyme is not detectable until the eighth week of
150 pregnancy [32].

151 We identified several sources of variation in tALP. The observed elevated tALP in
152 women with cholestasis, other liver diseases, or who have a multiple pregnancy was
153 as expected. Regarding chronic histiocytic intervillitis, we previously reported an
154 increase in tALP >600 IU/L in 10 out of a sample of 18 women with this condition
155 [15]. The tALP elevation we observed again in the present study merits further

156 evaluation. Regarding preeclampsia, we found herein a significant tALP elevation, at
157 1.12 MoM. This is valuable, in part, because these are the first solid data on this topic
158 to date. After initial descriptive and nonquantitative investigations [5,6], various
159 studies have indicated a decrease in tALP in cases of hypertension or preeclampsia
160 [7,9], sometimes without objective evidence [8,10]. More recent studies have not
161 shown ALP changes in preeclampsia, from either total serum ALP or placental ALP
162 measured in saliva [11,12].

163 We also showed a highly significant discrete tALP elevation among women whose
164 infants were SGA (1.08 MoM). To our knowledge, this is another novel finding. Apart
165 from a reported case of severe SGA with very high total antenatal ALP [14], a
166 statistical link between ALP levels and low birth weight for gestational age has not
167 been shown before. Although an increased risk of delivering an infant weighing
168 <2500 g was demonstrated in the case of tALP ≥ 2 MoM in the second trimester, it is
169 impossible to determine from these studies [2,13] whether this birth weight was
170 related to delivery before 37 weeks gestational age or to actual growth restriction
171 [3,4,33].

172 Similarly, we found a small but significant elevation of tALP with smoking during
173 pregnancy (1.10 MoM). However, only a few studies have been reported, and they
174 included small samples (i.e., $N < 50$). Two of these failed to find an association
175 between maternal smoking and tALP [34,35], and one study showed a significant
176 increase in placental isoenzyme during the third trimester among patients who
177 smoked [36]. While the mechanism of this increase is unknown, we speculate that
178 placental hypoxia—linked to CO levels among smokers—may be involved with
179 increased placental capillarization [37].

180 Apart from contradictory and isolated unexplained increases >1000 IU/L [38–41],
181 there are few data in the literature with which to compare our finding of a very small
182 decrease in tALP with gestational diabetes. In one modest-sized case–control study,
183 ALP levels were unaltered during the first trimester in gestational diabetes cases [42].
184 In contrast, a large prospective Chinese study (N=2073 patients) showed a
185 significant increase in gestational diabetes risk with higher serum ALP before 20
186 days gestation [43].

187 In sum, we found that tALP increased with chronic histiocytic intervillitis,
188 preeclampsia, SGA, and maternal smoking, and slightly decreased in gestational
189 diabetes, reflecting sometimes very small yet statistically significant variations.
190 Although most of these associations are not necessarily clinically meaningful, they
191 provide valuable knowledge. Establishing reference standards at each gestational
192 age may enable a better understanding of potential diagnostic or prognostic roles of
193 tALP values (e.g., in chronic histiocytic intervillitis). These findings also shed light
194 on the origins of increased tALP during pregnancy. Whereas tALP is elevated in all
195 placental hypoxia circumstances (i.e., preeclampsia, SGA, and maternal smoking),
196 its rise may reflect an increase in activity and/or surface of the syncytiotrophoblast in
197 these conditions, as the placental isoenzyme is mainly produced at this level [44].
198 tALP values may also reflect an increased release of placental microvesicles and
199 exosomes containing ALP from the placental surface [44–47]. Conversely, the
200 significance of decreased ALP in gestational diabetes is unknown. We hypothesize
201 that it may be related to the delayed placental maturation observed in this condition
202 [48].

203 A primary limitation of this study is its retrospective nature. The pregnant women in
204 this sample had a tALP blood test without our knowing its precise reason (i.e.,

205 whether it was systematic-based). We tried to limit this selection bias by excluding
206 the main known pathologies likely to modify tALP values. Further, our sample was
207 generally characterized as low risk in terms of prematurity (8.6%), cesarean delivery
208 (21.5%), and macrosomia (7.6%), all of which are similar to the rates observed in our
209 country during the most recent (2016) nationally representative birth survey
210 (prematurity, 7.5%; cesarean section, 20.4%; birth weight >4000 g, 6.8% [49]).

211 Another limitation of our study is that tALP measured during pregnancy is the sum of
212 hepatic, bone, placental, renal, intestinal and germinal ALP [1]. It is possible that
213 some placental diseases are accompanied by more noticeable variations in placental
214 ALP (PLAP) than tALP. As the determination of PLAP is more complex and
215 expensive than that of tALP, their normal evolution during pregnancy should be the
216 subject of studies specifically designed for this purpose.

217 In conclusion, our large population-based sample allowed us to establish tALP
218 reference curves based on gestational age. These findings warrant further
219 investigation to establish whether tALP level may be a direct or indirect reflection of
220 the activity and/or surface of the syncytiotrophoblast, the main site of synthesis of
221 placental isoenzyme [44].

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Table 1. Characteristics of the 2415 pregnancies included in the study

	Median [IQ25; IQ75] n (%)
Maternal age	30.0 [26.0 ; 34.0]
Smoking during pregnancy (n=1839)	235 (12.8)
No previous pregnancy	1025 (42.4)
Pre-existing hypertension during pregnancy	51 (2.1)
Hospitalization during pregnancy	1393 (57.7)
Prematurity < 37 WG	208 (8.6)
Gestational age at delivery	39.7 [38.7 ; 40.7]
Cesarean section	519 (21.5)
Birthweight	3340 [3000 ; 3650]
Macrosomia > 4000 g	184 (7.6)

Table 2. Distribution of total alkaline phosphatase among the 2415 included pregnancies (IU/L)

These values were obtained after smoothing (see materials and methods)

SA	2 - 22 SA (percentile)					SA	23 - 41 (percentile)				
	2.5	10	50	90	97.5		2.5	10	50	90	97.5
2	34	43	70	125	177	22	36	44	68	110	147
3	32	41	66	115	162	23	37	45	70	114	152
4	31	39	63	108	151	24	38	47	72	118	158
5	30	38	60	103	143	25	40	49	75	123	164
6	30	37	59	100	137	26	41	51	78	128	171
7	29	37	57	97	132	27	43	53	81	133	179
8	29	36	57	95	129	28	45	55	85	140	188
9	29	36	56	93	127	29	46	57	89	147	198
10	29	36	56	92	125	30	49	60	93	155	209
11	29	36	56	92	124	31	51	63	98	163	221
12	29	36	56	92	124	32	53	66	103	173	234
13	30	36	56	92	124	33	56	70	109	183	249
14	30	37	57	93	125	34	59	74	116	195	266
15	30	37	57	94	126	35	63	78	123	208	285
16	31	38	58	95	127	36	66	83	131	223	307
17	32	39	59	97	129	37	70	88	140	240	331
18	32	40	61	99	132	38	75	94	150	258	358
19	33	41	62	101	135	39	80	100	161	279	389
20	34	42	64	104	138	40	85	107	173	303	424
21	35	43	66	107	142	41	91	115	187	330	465

Table 3. Factors influencing alkaline phosphatase levels in pregnant women
(IUD In utero death ; TOP Termination of pregnancy)

	MoM [IQ25-IQ75]	p
Included pregnancies (n=2415)	0.96 [0.79 ; 1.24]	
Chronic Histiocytic Intervillositis (n=28) ^(a)	1.61 [1.22 ; 2.86]	< 0.001
Cholestasis (n=328) ^(a)	1.43 [1.04 ; 1.90]	< 0.001
Multiple pregnancies (n=358) ^(a)	1.32 [0.96 ; 1.79]	< 0.001
Other liver diseases (n=38) ^(a)	1.31 [1.00 ; 2.06]	< 0.001
Preeclampsia (n=812) ^(a)	1.12 [0.88 ; 1.51]	< 0.001
Smoking (n=235) ^(b,c)	1.10 [0.86 ; 1.45]	< 0.001
Small for Gestational Age (n=707) ^(a)	1.08 [0.88 ; 1.51]	< 0.001
IUD and TOP (n=120) ^(a)	1.01 [0.82 ; 1.34]	0.148
Prepregnancy diabetes (n=417) ^(a)	1.00 [0.80 ; 1.32]	0.067
Gestational diabetes (n=2873) ^(a)	0.95 [0.78 ; 1.18]	0.036
Previous hypertension (n=51) ^(b)	0.91 [0.77 ; 1.22]	0.66

a- Compared to the 2415 included pregnancies

b- Comparison within included pregnancies

c- 576 missing values for tobacco use during pregnancy

Figure 1: Flow chart of the study
 * Several possible exclusion criteria

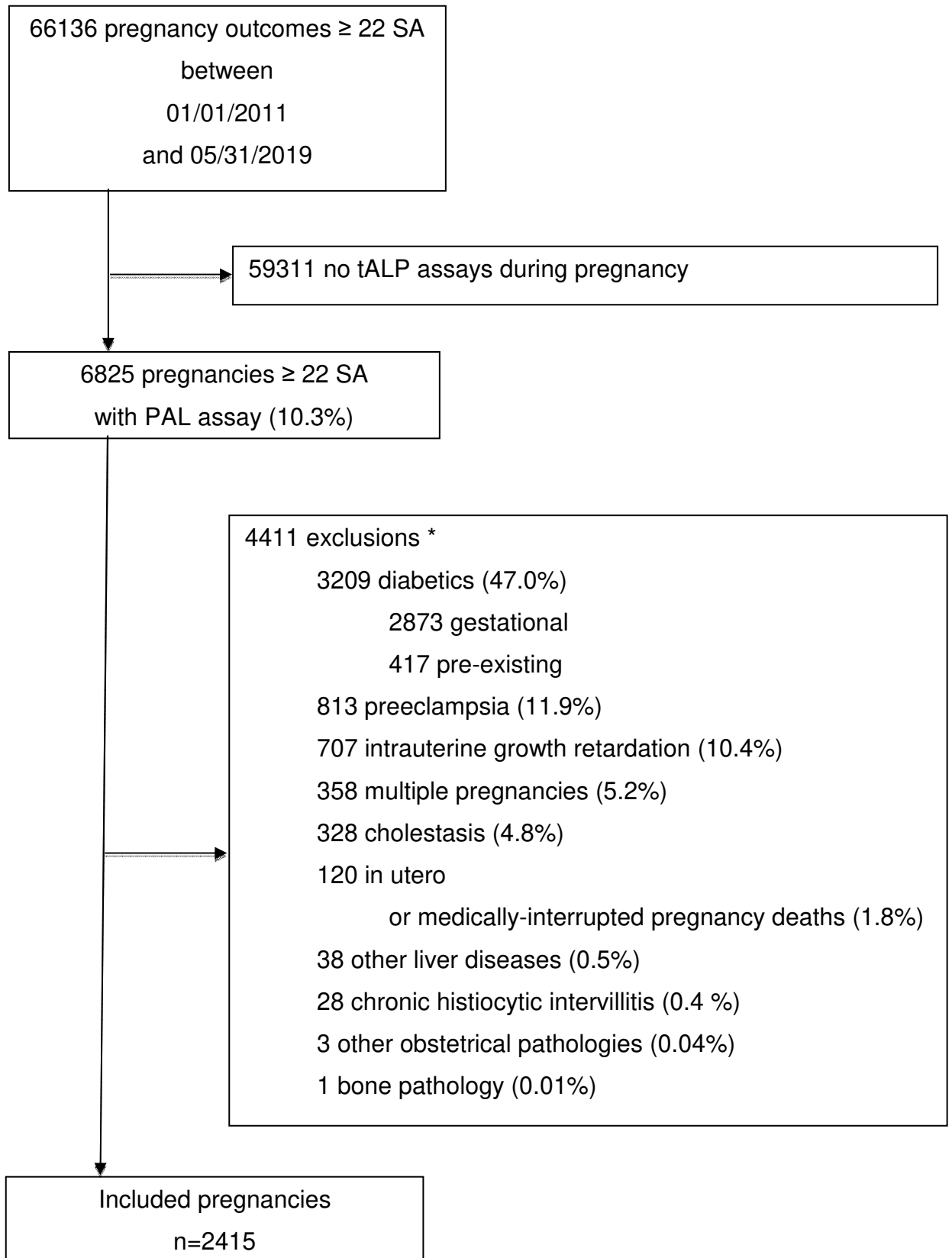
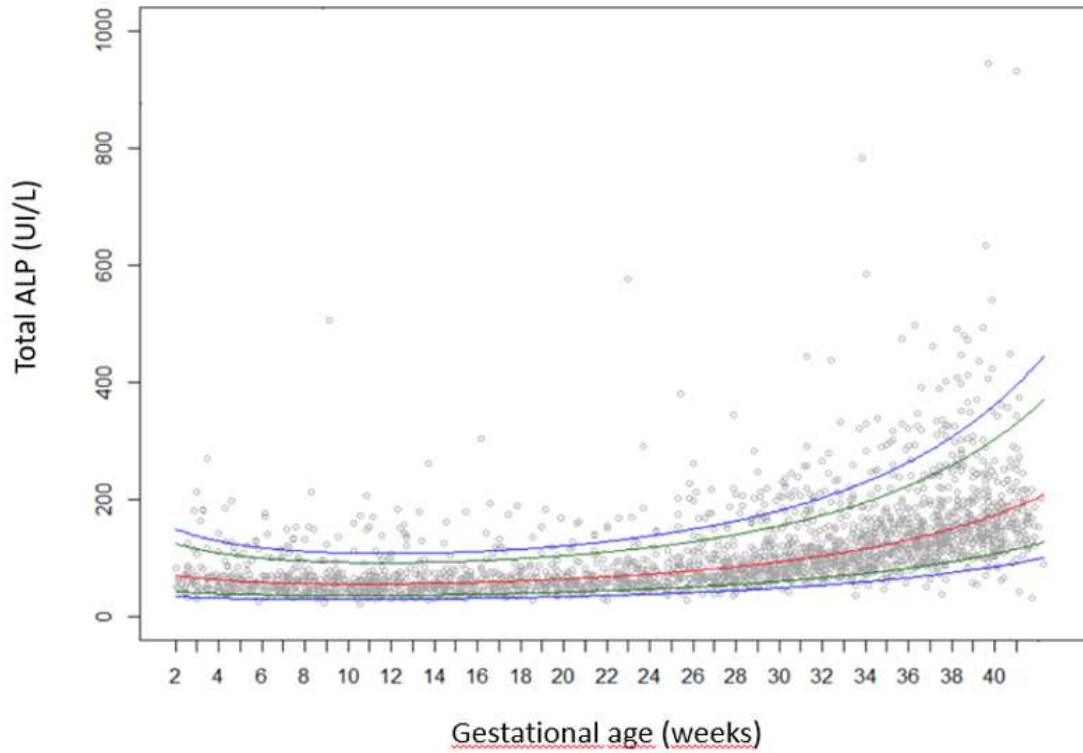


Figure 2. Distribution of total alkaline phosphatase (tALP) values by gestational age among the 2415 included pregnancies.

The solid line curves represent the 2.5th, 10th, 50th, 90th and 97.5th percentiles obtained after modeling (from bottom to top). The median is shown in red.



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