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Placental weight centiles adjusted for age, parity and fetal sex

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ABSTRACT

Introduction: The weight of the placenta can be indicative of efficacy in nutrient and oxygen supply. Furthermore, it has been suggested that a measure of the placenta's ability to adequately supply nutrients to the fetus can be found in the relationship between birth weight and placental weight expressed as a ratio. Our aim was to develop age adjusted placenta weight and birth weight to placenta weight ratio reference curves that are stratified by maternal parity and fetal sex.

Methods: We included singleton, non-anomalous births with a gestational age inclusive of 28 + 0 weeks to 42 + 6 weeks. Excluded were pregnancies of multiplicity, fetuses with congenital abnormalities, stillbirths and pregnancies that had placental complications (ie placenta previa or abruption). Generalised additive model for location, shape and scale (GAMLSS) was used to fit reference curves.

Results: We stratified 97,882 pregnancies by maternal nulliparity status and fetal sex. Extensive assessment model goodness-of-fit showed appropriate modeling and accurate fit to the four parameters of distribution. Our results show accurate model fit of the reference curves to the data. We demonstrated that the influence that parity has on the placenta weight is far greater than that exerted by fetal sex, and that the difference is dependent on gestational age.

Discussion: This is the largest presentation of age and parity adjusted placenta weight and feto-placental weight ratio reference ranges to date. The difference observed between nulliparous and multiparous pregnancies could be explained by biological memory and the remnants of maternal endo-myometrial vascularity after the first pregnancy.

1. Introduction

Designated with supplying nutrients and protection from the external environment, a well-functioning placenta is vital for the well-being of the fetus [1–3]. The weight of the placenta can be indicative of efficacy in nutrient and oxygen supply. Low weight suggests poor placentation whereas a higher weight may be the result of maternal diabetes or pregnancy weight gain. Both abnormalities have been identified as risk factors for adverse outcomes in the mother and fetus as well as longer-term neonate and child outcomes. Low placental weight is more prevalent amongst stillbirths and fetal growth restriction, and a high placental weight amongst neonatal deaths and low Apgar scores [2–7]. Furthermore, it has been suggested that a measure of the placenta's ability to adequately supply nutrients to the fetus can be found in the relationship between birth weight and placental weight expressed as a ratio [2,4–7].

While the weight of the placenta is influenced by several biological and environmental factors, the fetal sex and maternal parity are the most consistent causes of diversity in healthy placentas with parity having larger effects than fetal sex [6]. Fetal sex has long been known to have an

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effect on placenta weight, with known sex-specific placental gene expression, as well as sex specific differences in biomarkers and placental gene-environment interactions [8]. More recently there has been increasing attention to the impact that parity has on placentation. Several biological studies have provided evidence of mothers maintaining the restructuring of maternal spiral arteries and retaining a biological memory after the first pregnancy that assists placentation in subsequent pregnancies [8–13].

The influence that parity has on placenta weight has largely been ignored in the creation of reference ranges for both placenta weight and feto-placental ratio. As exceptions, Wallace et al. and Ogawa et al. have produced reference centiles adjusted for gestational age, parity and fetal sex which illustrated that nulliparity has a greater influence on placenta weight than the effect of fetal sex [6,7]. While several reference curves have been created for placental weight, only these two studies have stratified the curves based on both of these parameters [6,7]. However, they report conflicting findings for the relationship between parity and birth weight to placenta weight ratio [6,7].

The importance of reference ranges is two-fold: they are used for both clinical and research purposes. Clinically we rely on accurate reference for comparisons to "normal". In research we spend untold amounts of time and resources to ensure accuracy of our study design, recruitment and methodology. It is therefore imperative that reference ranges adjust for known interaction effects and reflect the wider population with as much precision as possible.

In an attempt to resolve the conflicting findings from Wallace et al. and Ogawa et al. we employ a cohort that is much larger than Ogawa's. While the Moba cohort is similar in size to Wallace's it is collected over a much shorter time period of 10 years (compared to 30 years for Wallace et al.), thus reducing the exposure to secular trends in maternal age, parity etc. as well as other potential unexamined temporal influences. Furthermore, we utilise the Generalised Additive Model for Location, Shape and Scale - an extension from the esteemed LMS method used in both previous papers [14]. Our aim was to develop age adjusted placenta weight and birth weight to placenta weight ratio reference curves that are stratified by parity and fetal sex in a large Scandinavian cohort.

2. Methodology

We used cross sectional data from The Norwegian Mother, Father and Child Cohort Study (MoBa) for pregnancies recorded between 1999 and 2009 [15]. In short, MoBa is a population-based pregnancy cohort study conducted by the Norwegian Institute of Public Health. Participants were recruited from all over Norway from 1999 to 2008. The women consented to participation in 41% of the pregnancies. The cohort now includes 114,500 children, 95,200 mothers and 75,200 fathers. The current study is based on version 10 of the quality-assured data files released for research. The establishment of MoBa and initial data collection was based on a license from the Norwegian Data Protection Agency and approval from The Regional Committees for Medical and Health Research Ethics. The MoBa cohort is now based on regulations related to the Norwegian Health Registry Act. The current study was approved by The Regional Committees for Medical and Health Research Ethics in South-Eastern, Norway.

Women in MoBa were matched against their entries from the Norwegian Medical Birth Registry. The Norwegian Medical Birth Registry is a compulsory birth registry that collects information for all births greater than 12 weeks gestation. Routine data is collected on (but not restricted to), pregnancy or birth complications as well as pre-pregnancy and intra-pregnancy maternal health, placenta weight and birth weight.

We included singleton, non-anomalous births with a gestational age inclusive of 28 + 0 weeks to 42 + 6 weeks. The gestational age was restricted due to the four-way stratification of the study sample, outside of these parameters the insufficient numbers made the models unstable.

Anomalies excluded from analysis included fetuses with congenital abnormalities, stillbirths, and pregnancies with placental complications which may affect the accuracy of the weighing of the placenta (i.e., placenta previa, abruption, manual extraction or curettage). Placentas were weighed with membranes and umbilical cord attached. For the placental weight centiles, pregnancies that had missing data for either placental weight or gestational age at birth were also removed from the study cohort. This was extended to include missing data on birth weight for the feto-placenta weight ratio analysis. Institutional ethical approval was granted through the Norwegian Ethical Committee West Region (University of Bergen) REK 2012/67.

3. Statistical analysis

Demographic data were reported as proportions (n) for categorical data, mean and standard deviation were provided for continuous data. The feto-placenta weight ratio is the simple division of the fetal birth weight divided by the placenta weight.

For the exclusion of outliers and extreme values, initial centiles for both placenta weight and birth weight were created using the Generalised Additive Model for Location, Shape and Scale (GAMLSS). From these Z-scores were calculated which enabled us to exclude any values that were greater than 3.5 standard deviations from the mean - which excludes the top and bottom 0.05 percentiles.

To test appropriateness of the stratification by sex and nulliparity, interaction terms of gestational duration for sex and nulliparity were first included in a GAMLSS model and tested. Gestational age adjusted placenta weight and feto-placenta weight ratio centiles were then calculated using GAMLSS for the relevant stratifications. The most appropriate normalisation of the data was obtained after assessment of the Normal, Box-Cox Cole and Green (BCCG), Box-Cox *t* (BCT), and Box-Cox Power Exponential distributions. Cubic splines, penalised basis spline, polynomial and fractional polynomial smoothing methods were all evaluated. Appraisal of the model fit was based on the Akaike Information Criterion (AIC) with consideration to the Schwartz Bayesian Criterion, Global Deviance and visual assessment of the centile graphs. Assessment of the residuals and goodness-of-fit were performed using graphical representations using Q-Q plots and worm plots. Summary statistics of the parameters of distribution for the residuals are also reported.

All data manipulation and statistical analysis was performed using R (Version 3.6.3) and the model algorithm using the GAMLSS package by Rigby and Stasinopolous [14].

4. Results

There were a total 114,728 births captured in MoBa between 1999 and 2009, of which 97,946 (85.4%) met the inclusion criteria. Of those excluded, 4,406/114,728 (3.5%) had missing placental weights, 446/110,682 (0.4%) had missing gestational age, 3,795/110,236 (3.4%) were plural births, 284/106,441 (0.02%) were stillbirths, 5,017/106,157 (5.7%) had congenital abnormalities, 2,830/101,140 (2.8%) had placental complications and 362/98,308 (0.04%) were outside the gestational age restriction. Removal of outliers (64/97,946 [0.07%]) left a study cohort consisting of 97,882 (85.3%) pregnancies, including - 22.3% (21,820/97,882) male fetuses of nulliparous women and 28.8% (28,210/97,882) male fetuses of multiparous women, 21.2% (20,765/97,882) female fetuses of nulliparous women and 27.7% (27,087/97,882) female fetuses of multiparous women. The mean placenta weight of the study cohort was 678 (145.3) grams.

Assessment of the appropriateness of stratification by sex and parity found significant interactions between gestational age and sex ($p = 0.004$) as well as between gestational duration and nulliparity ($p = 3.85e\text{-}13$) (Supplemental Fig. 1).

After assessment of the various distributions, the most appropriate was the BCT. With the use of this distribution applied to our data, we found it sufficient to model only the mean parameter using a fractional

polynomial smoothing term. Inclusion of scale or shape distribution parameters (standard deviation, skewness or kurtosis) did not improve the model fit. The centiles show an increasing placental weight throughout the gestational age period with a proportional increase in variance over the same period. The curves have a smooth increasing trend with no decrease or deviations from the expected values based on the trajectory of the curves. Values of the centiles at each week, for each strata can be found in Tables 1–4 and graphical representations seen in Fig. 1 and Supplementary Figs. 2–4. The tables of centiles for each strata report the placenta weight (or feto-placental ratio) that is calculated for the 3rd, 5th, 10th, 25th, 50th, 75th, 90th, 95th and 97th percentile per gestational week, along with the number (N) of measures used to calculate at individual weeks. The graphical representations of the centiles in Fig. 1 and Supplemental Figs. 2–4 display scatterplots of the placenta weight (or feto-placental ratio) against gestational age with a different color representing a different percentile. The percentiles reported graphically are for the 0.4th, 2nd, 10th, 25th, 50th, 75th, 90th, 98th and 99.6th percentiles. The difference in reporting of the percentiles is due to the tables reflecting those more commonly used in reporting or research while those used in the plots help describe the distributions of the data more comprehensively.

Values of percentiles per day can be found in Supplementary Excel Spreadsheets.

Goodness of fit tests showed appropriate data distribution and fitting for all four parameters of distribution with results shown in Supplemental Tables 1 and 2 Graphical representations of residual plots can be found in Fig. 2 and Supplemental Figs. 5–11, with worm plots in Supplemental Figs. 12–19.

Supplemental Tables 1 and 2 give the statistics for the modeling for each parameter of distribution (mean, variance, skewness and kurtosis). The gold standard statistic for each parameter is a mean of 0, variance of 1, skewness of 0 and kurtosis of 3. The right side of Supplementary Tables 1 and 2 report the percentage of cases that are captured by each percentile (e.g. the 10th centile should capture 10% of the sample).

The residual plots assess the adequacy of the model fit through assessment of the residuals. The top two plots of Fig. 2 (and Supplementary Fig. 5 -11) graph the residuals against the fitted values in the left graph and the residuals against an index in the right graph. Both should have the residuals scattered randomly around zero (y axis) that would surmount to a reasonably normal distribution if plotted against each value of the x axis. All residual plots show that the residuals are scattered randomly against the fitted values and against the index for all strata of both placenta weight and for feto-placental ratio. The bottom left graph is a kernel density plot and should be a bell-shaped curve akin to a normal distribution. The bottom right is a normal Q-Q plot in which the values should fall along expected lines (in red). All kernel density plots resemble the normal distribution bell curve and there are only very slight deviations in the very tails from the expected curves in the Q-Q plots. The very slight deviations that can be observed in the male and female, multiparous mother's placenta weight goodness of fit plots (Supplementary Figs. 5 and 7) that can be attributed to a very small number of outliers which have not affected the overall fit of the models as evidenced by the goodness of fit statistics (Supplementary Table 1).

The worm plots (Supplementary Figs. 12–19) allow the assessment of how adequately the model is fitted to the data. The observation of quadratic or cubic shapes - S-curve or U-curve that trends towards the zero of the x axis and inside the lines of confidence (the U-shaped dotted lines), indicate inadequate correction of skewness or kurtosis. In all worm plots for each strata show good fitting of each model with only very slight deviations inside the lines of confidence.

Table 1
Placenta Weight Centiles for Male Fetuses by Gestational Age and Parity.

	Nulliparous Male										Multiparous Male									
Gestational Age	N	3%	5%	10%	25%	50%	75%	90%	95%	97%	N	3%	5%	10%	25%	50%	75%	90%	95%	97%
28+0	15	189.4	199.5	215.6	244.4	279.8	319.9	361.2	389.0	408.5	10	216.5	227.8	245.8	278.3	318.6	364.4	411.5	443.0	465.0
29+0	14	218.8	230.4	249.0	282.3	323.2	369.5	417.2	449.3	471.8	19	245.2	257.9	278.3	315.2	360.8	412.6	465.9	501.6	526.6
30+0	25	245.8	258.9	279.8	317.2	363.1	415.1	468.8	504.8	530.2	24	272.3	286.4	309.0	349.9	400.6	458.1	517.3	557.0	584.7
31+0	36	270.9	285.3	308.3	349.5	400.1	457.4	516.6	556.3	584.2	28	297.8	313.2	338.0	382.7	438.1	501.0	565.8	609.2	639.5
32+0	62	294.2	309.9	334.9	379.6	434.6	496.9	561.1	604.3	634.6	49	321.8	338.5	365.3	413.6	473.5	541.5	611.5	658.3	691.1
33+0	91	316.1	332.9	359.8	407.9	467.0	533.9	602.9	649.3	681.8	77	344.4	362.2	390.9	442.7	506.7	579.5	654.4	704.6	739.6
34+0	148	336.8	354.7	383.3	434.5	497.5	568.7	642.3	691.7	726.4	102	365.6	384.5	415.0	469.9	537.9	615.1	694.7	747.9	785.1
35+0	229	356.3	375.3	405.6	459.8	526.4	601.8	679.6	731.9	768.6	215	385.4	405.4	437.5	495.4	567.1	648.5	732.4	788.5	827.7
36+0	470	375.0	394.9	426.8	483.9	554.0	633.3	715.2	770.2	808.8	471	403.9	424.9	458.5	519.2	594.3	679.7	767.5	826.4	867.5
37+0	925	392.9	413.8	447.2	506.9	580.4	663.5	749.3	806.9	847.4	1092	421.2	443.0	478.1	541.3	619.7	708.7	800.3	861.6	904.5
38+0	2166	410.1	431.9	466.8	529.2	605.8	692.6	782.1	842.3	884.5	3343	437.1	459.8	496.2	561.9	643.2	735.5	830.7	894.3	938.8
39+0	4393	426.8	449.5	485.8	550.7	630.4	720.7	813.9	876.5	920.5	6204	451.9	475.3	513.0	580.9	664.9	760.4	858.7	924.5	970.5
40+0	6068	443.0	466.5	504.2	571.6	654.4	748.1	844.8	909.8	955.4	8427	465.5	489.6	528.4	598.3	684.9	783.3	884.5	952.3	999.7
41+0	4799	458.8	483.2	522.2	592.0	677.8	774.9	875.0	942.3	989.6	6017	477.9	502.7	542.5	614.3	703.2	804.2	908.2	977.7	1026.4
42+0	2379	474.3	499.6	539.9	612.1	700.7	801.1	904.6	974.2	1023.1	2132	489.2	514.6	555.4	628.8	719.8	823.2	929.7	1000.9	1050.7

Table 2
Placenta Weight Centiles for Female Fetuses by Gestational Age and Parity.

	Nulliparous Female										Multiparous Female									
Gestational Age	N	3%	5%	10%	25%	50%	75%	90%	95%	97%	N	3%	5%	10%	25%	50%	75%	90%	95%	97%
28+0	13	226.6	238.5	257.7	292.2	334.7	383.0	432.9	466.4	490.0	11	213.5	225.1	243.5	276.4	316.9	363.3	411.8	444.8	468.3
29+0	13	243.7	256.5	277.2	314.2	360.0	411.9	465.6	501.6	527.0	6	244.4	257.6	278.7	316.3	362.8	415.8	471.3	509.2	536.1
30+0	28	261.5	275.3	297.5	337.2	386.3	442.1	499.7	538.4	565.6	18	272.4	287.1	310.6	352.5	404.3	463.4	525.3	567.5	597.4
31+0	31	279.8	294.6	318.3	360.8	413.3	473.0	534.6	576.0	605.1	18	297.9	313.9	339.6	385.5	442.1	506.7	574.4	620.5	653.3
32+0	52	298.2	314.0	339.3	384.6	440.6	504.2	569.9	614.0	645.1	32	321.1	338.4	366.1	415.6	476.6	546.3	619.2	668.9	704.3
33+0	83	316.7	333.4	360.3	408.4	467.9	535.4	605.1	652.1	685.0	64	342.4	360.9	390.4	443.2	508.2	582.6	660.3	713.4	751.0
34+0	126	335.0	352.7	381.1	432.1	495.0	566.4	640.1	689.8	724.6	118	362.1	381.6	412.8	468.6	537.4	615.9	698.2	754.2	794.1
35+0	220	353.1	371.8	401.7	455.4	521.6	596.9	674.7	727.0	763.7	197	380.2	400.7	433.5	492.0	564.3	646.8	733.1	792.0	833.8
36+0	402	370.8	390.4	421.9	478.2	547.9	626.9	708.6	763.5	802.1	442	397.0	418.4	452.6	513.8	589.2	675.4	765.5	827.0	870.7
37+0	947	388.2	408.7	441.6	500.6	573.5	656.2	741.7	799.2	839.6	1178	412.6	434.9	470.4	534.0	612.4	701.9	795.6	859.6	904.9
38+0	2346	405.1	426.5	460.9	522.5	598.5	684.9	774.1	834.1	876.2	3569	427.2	450.2	487.1	552.9	634.1	726.8	823.8	889.9	936.9
39+0	4830	421.6	443.9	479.6	543.7	622.9	712.7	805.6	868.0	911.9	6922	440.9	464.6	502.6	570.6	654.3	750.0	850.1	918.4	966.9
40+0	6070	437.6	460.8	497.8	564.4	646.5	739.8	836.2	901.0	946.5	8269	453.7	478.2	517.3	587.2	673.4	771.8	874.9	945.1	995.0
41+0	4116	453.2	477.1	515.5	584.4	669.5	766.1	865.9	933.0	980.1	4876	465.8	490.9	531.1	602.8	691.3	792.4	898.2	970.3	1021.6
42+0	1488	468.2	493.0	532.7	603.9	691.7	791.5	894.7	964.0	1012.7	1367	477.2	503.0	544.1	617.6	708.3	811.9	920.2	994.1	1046.6

In comparison of the strata, the mean difference in placenta weight in the male fetal cohorts for the multiparous mothers compared to the nulliparous mothers were: 10th centile 28.2 g (sd 4.7), 50th centile 35.9g (sd 6.2), 90th centile 46.6g (sd 8.0). For the female cohort the placental weight differences by parity were: 10th centile 19.8g (sd 12.9), 50th centile 27.0g (sd 16.9), 90th centile 38.2g (sd 22.2). The mean differences in placenta weight in the nulliparous mothers for the male cohort compared to the female cohort were: 10th centile −3.6g (sd 14.9), 50th centile −5.0g (sd 19.2), 90th centile −7.7g (sd 24.6). For the multiparous mothers, the mean differences of male fetuses to female fetuses were: 10th centile 4.8g (sd 5.1), 50th centile 3.8g (sd 6.1), 90th centile 0.7 g (sd 7.0) (Supplementary Table 3).

The centiles that we have created have slight differences to those published by Wallace et al. and Ogawa et al. Our centiles have a smoother profile to the curves as well as a more defined increasing variance with the progression of gestational age. After 36 weeks gestation, our centiles are slightly higher than those produced by both Wallace et al. and Ogawa et al. Graphical representations of these comparisons can be found in Supplemental Fig. 20.

Thompson et al. had previously created centiles for placenta weight but stratified for only sex using the Norweigian Medical Birth Registry [11] and comparison between these centiles and our results show good congruence particularly for the MoBa multiparous mothers (Supplementary Fig. 20). Where they do differ is in the smoothness of our centile curves compared to those produced by Thompson et al. [16].

5. Discussion

This is the largest presentation of age and parity adjusted placenta weight and feto-placental weight ratio reference ranges to date and the first for a Scandinavian cohort. The placenta weight percentiles were reflective of what Wallace et al. and Ogawa et al. found, placenta weight was greater for both male and female fetuses, across the entire gestational period in the multiparous cohort, with difference diminishing in the late term cohort [6,7]. In contrast to Wallace et al., but in line with Ogawa et al., for the feto-placental weight ratio we also found a significant difference between sexes in the nulliparous and multiparous cohorts [6,7].

The centiles that we have created have slight differences to those published by Wallace et al. and Ogawa et al. Our centiles have a smoother profile to the curves as well as a more defined increasing variance with the progression of gestational age. After 36 weeks gestation, our centiles are slightly higher than those produced by both Wallace et al. and Ogawa et al. Graphical representations of these comparisons can be found in Supplemental Fig. 20. These distinctions may be explained partially by the contrasts in cohorts' characteristics. Wallace et al. has a similar sample size to our study, however the study period expands over 30 years, exposing it to secular trends of maternal age, parity and other unexamined temporal influences. Ogawa et al. had a smaller study sample over a two-year period with strict inclusion criteria, which may have produced a selection bias. There were also differences in the measurement of placenta weight between the studies. All three studies weighed untrimmed placentas, however variations between the studies could also be partially due to the timing, differences in collection methods of the placenta (e.g., removal of clots etc.) and in the case of Wallace et al. rounding to the nearest 10g.

The influence of fetal sex on placenta weight has been well documented, with most reference curves adjusting for fetal sex and

Table 3
Feto-Placental Weight Ratio Centiles for Male Fetuses by Gestational Age and Parity.

	Nulliparous Male										Multiparous Male									
Gestational Age	N	3%	5%	10%	25%	50%	75%	90%	95%	97%	N	3%	5%	10%	25%	50%	75%	90%	95%	97%
28	14	2.36	2.46	2.61	2.88	3.21	3.57	3.93	4.17	4.33	10	2.20	2.29	2.43	2.68	2.98	3.31	3.65	3.87	4.02
29	14	2.54	2.65	2.81	3.11	3.46	3.85	4.24	4.49	4.67	16	2.39	2.49	2.64	2.92	3.25	3.61	3.97	4.21	4.38
30	24	2.72	2.84	3.01	3.33	3.70	4.12	4.54	4.81	5.00	22	2.58	2.69	2.86	3.15	3.50	3.89	4.29	4.55	4.73
31	34	2.90	3.02	3.21	3.54	3.94	4.38	4.83	5.12	5.32	26	2.77	2.88	3.06	3.38	3.76	4.18	4.60	4.88	5.07
32	60	3.06	3.19	3.39	3.75	4.17	4.64	5.11	5.41	5.62	48	2.95	3.07	3.26	3.60	4.01	4.45	4.90	5.19	5.40
33	89	3.22	3.36	3.57	3.94	4.39	4.88	5.37	5.69	5.92	72	3.12	3.25	3.46	3.81	4.24	4.71	5.19	5.50	5.72
34	148	3.38	3.51	3.74	4.12	4.59	5.11	5.62	5.96	6.19	99	3.29	3.43	3.64	4.02	4.47	4.97	5.47	5.80	6.03
35	229	3.52	3.66	3.89	4.30	4.78	5.32	5.86	6.21	6.45	213	3.45	3.59	3.82	4.21	4.68	5.20	5.73	6.07	6.31
36	468	3.64	3.79	4.03	4.45	4.96	5.51	6.07	6.43	6.68	470	3.59	3.74	3.98	4.39	4.88	5.43	5.97	6.33	6.58
37	921	3.76	3.91	4.16	4.59	5.11	5.68	6.26	6.63	6.89	1089	3.73	3.88	4.13	4.55	5.07	5.63	6.20	6.57	6.83
38	2159	3.86	4.01	4.27	4.71	5.25	5.83	6.42	6.81	7.07	3334	3.85	4.01	4.26	4.70	5.23	5.81	6.40	6.78	7.05
39	4385	3.94	4.10	4.36	4.81	5.36	5.96	6.56	6.95	7.22	6190	3.96	4.12	4.38	4.83	5.37	5.97	6.57	6.97	7.24
40	6056	4.00	4.17	4.43	4.89	5.44	6.05	6.66	7.06	7.34	8410	4.04	4.21	4.48	4.94	5.49	6.10	6.72	7.12	7.41
41	4788	4.04	4.21	4.48	4.94	5.50	6.12	6.74	7.14	7.42	6006	4.11	4.29	4.55	5.02	5.59	6.21	6.84	7.25	7.54
42	2375	4.07	4.23	4.50	4.97	5.53	6.15	6.77	7.18	7.46	2129	4.17	4.34	4.61	5.09	5.66	6.29	6.92	7.34	7.63

gestational age [16–19]. In this study, we have been able to demonstrate that the influence that parity has on the placenta weight is far greater than that exerted by fetal sex, but also interestingly we found that the difference is dependent on gestational age. Both these findings could be reflective of what happens at the very beginning of pregnancy during placentation.

Primiparity has previously been found to have negative implications on the growth of the placenta and subsequent growth of the fetus [20,21]. A woman's first pregnancy is twice as likely to end in stillbirth and has a higher maternal risk of suffering preeclampsia [9,22–24]. Importantly, first born fetuses tend to have lower birth weights and are more likely to be small for gestational age and/or growth restricted - often as a result of an ineffective placenta [20,21]. Inadequate placental size and function are often attributed to poor maternal revascularisation in the nulliparous pregnancy. Subsequent pregnancies benefit from permanent restructuring of the maternal spiral arteries and a biological memory that exists as a result of previous pregnancy [9–11].

The process of revascularisation plays a complex but intrinsic role in human haemochorial placentation. Trophoblastic cells need to successfully infiltrate both the endometrium and myometrium to enable alterations to the maternal uterine spiral arteries [12,13]. Maternally, this is preceded by the disruption of the internal elastic lamina of maternal vessels after infiltration of myointimal of cells through small fenestrations, in readiness for the trophoblastic cell invasion of the endometrial capillaries of the maternal spiral arteries [12,13,25,26]. Khong et al. suggests that some of these alterations in the maternal endo and myometrial vascularity remain after the first pregnancy which makes subsequent trophoblast invasion more successful [12].

Recent papers by Goldman-Wohl et al. and Gamliel et al. found that Natural Killer (NK) cells found in the decidua (dNK) were able to form epigenetic memory for subsequent pregnancies [9–11]. The dNK assists in the placental bed remodelling by encouraging trophoblast invasion and angiogenesis as well facilitating the revascularisation of the spiral arteries [9,10]. Goldman-Wohl et al. were able to show that once these dNK have been primed during the first pregnancy, they form an epigenetic memory which enables increased efficient and effective placental bed remodelling in the ensuing pregnancies [9,10].

Events enabling placentation during the first trimester decidua are critical for successful reproduction. Trophoblast invasion relies on adaptation of the inflammatory and immune responses that minimise reaction to the changes in the uterus, and subsequent placenta and fetal formation [27]. These physiological changes that happen as a result of pregnancy are not fully reversed after the completion of the pregnancy which allows for easier revascularisation, resulting in expediting access to vital nutrients in subsequent pregnancies [9,10]. This assists the growth of the placenta and fetus as well as beneficial long term metabolic and neurodevelopment of the child.

The findings of the strong effect of parity on placental weight reflect what has been found from biological studies for the priming of the endometrium and epigenetic memory. However, that is not to say that

Table 4
Feto-Placental Weight Ratio Centiles for Female Fetuses by Gestational Age and Parity.

	Nulliparous Female										Multiparous Female									
Gestational Age	N	3%	5%	10%	25%	50%	75%	90%	95%	97%	N	3%	5%	10%	25%	50%	75%	90%	95%	97%
28	11	2.13	2.22	2.36	2.61	2.91	3.23	3.56	3.78	3.93	11	2.20	2.29	2.43	2.68	2.98	3.31	3.65	3.87	4.02
29	12	2.36	2.46	2.62	2.89	3.22	3.58	3.94	4.18	4.34	5	2.39	2.49	2.64	2.92	3.25	3.61	3.97	4.21	4.38
30	27	2.58	2.68	2.86	3.15	3.51	3.90	4.30	4.56	4.74	18	2.58	2.69	2.86	3.15	3.50	3.89	4.29	4.55	4.73
31	29	2.78	2.90	3.08	3.41	3.79	4.22	4.64	4.92	5.12	17	2.77	2.88	3.06	3.38	3.76	4.18	4.60	4.88	5.07
32	50	2.97	3.10	3.30	3.64	4.05	4.51	4.96	5.26	5.47	30	2.95	3.07	3.26	3.60	4.01	4.45	4.90	5.19	5.40
33	82	3.15	3.29	3.50	3.86	4.30	4.78	5.26	5.58	5.80	64	3.12	3.25	3.46	3.81	4.24	4.71	5.19	5.50	5.72
34	126	3.32	3.46	3.68	4.06	4.52	5.03	5.54	5.87	6.11	116	3.29	3.43	3.64	4.02	4.47	4.97	5.47	5.80	6.03
35	219	3.47	3.61	3.84	4.25	4.73	5.26	5.79	6.14	6.38	197	3.45	3.59	3.82	4.21	4.68	5.20	5.73	6.07	6.31
36	399	3.60	3.75	3.99	4.41	4.91	5.46	6.01	6.37	6.62	439	3.59	3.74	3.98	4.39	4.88	5.43	5.97	6.33	6.58
37	943	3.71	3.87	4.12	4.55	5.06	5.63	6.20	6.57	6.83	1173	3.73	3.88	4.13	4.55	5.07	5.63	6.20	6.57	6.83
38	2338	3.81	3.97	4.22	4.66	5.19	5.77	6.35	6.74	7.01	3560	3.85	4.01	4.26	4.70	5.23	5.81	6.40	6.78	7.05
39	4823	3.88	4.04	4.30	4.75	5.29	5.88	6.48	6.87	7.14	6907	3.96	4.12	4.38	4.83	5.37	5.97	6.57	6.97	7.24
40	6060	3.93	4.10	4.36	4.82	5.36	5.96	6.56	6.96	7.24	8251	4.04	4.21	4.48	4.94	5.49	6.10	6.72	7.12	7.41
41	4107	3.96	4.13	4.39	4.85	5.40	6.00	6.61	7.01	7.29	4872	4.11	4.29	4.55	5.02	5.59	6.21	6.84	7.25	7.54
42	1486	3.97	4.13	4.40	4.86	5.41	6.01	6.62	7.02	7.30	1362	4.17	4.34	4.61	5.09	5.66	6.29	6.92	7.34	7.63

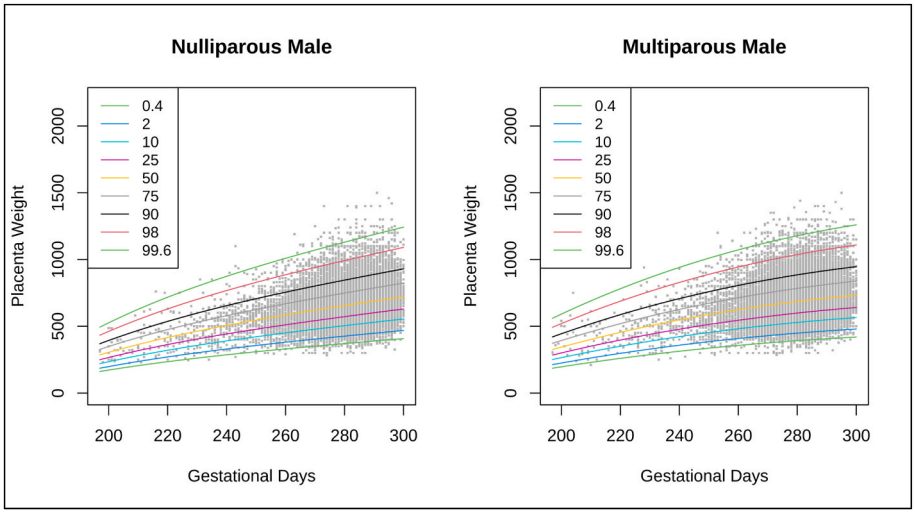

Fig. 1. Male placenta weight centiles by gestational age and maternal parity.

we should ignore the influence that sex also has on the placenta weight. Despite the overall effect of sex appearing to be lesser compared to that of parity, the sex-specific placental gene expression, and the differences in biomarkers and placental gene-environment interactions also influence the revascularisation process [8]. In fact, the influence of sex on revascularisation can have important differences especially in complicated pregnancies, with for example, the male fetus causing reduced microvascular vasodilatation in preeclamptic mothers in

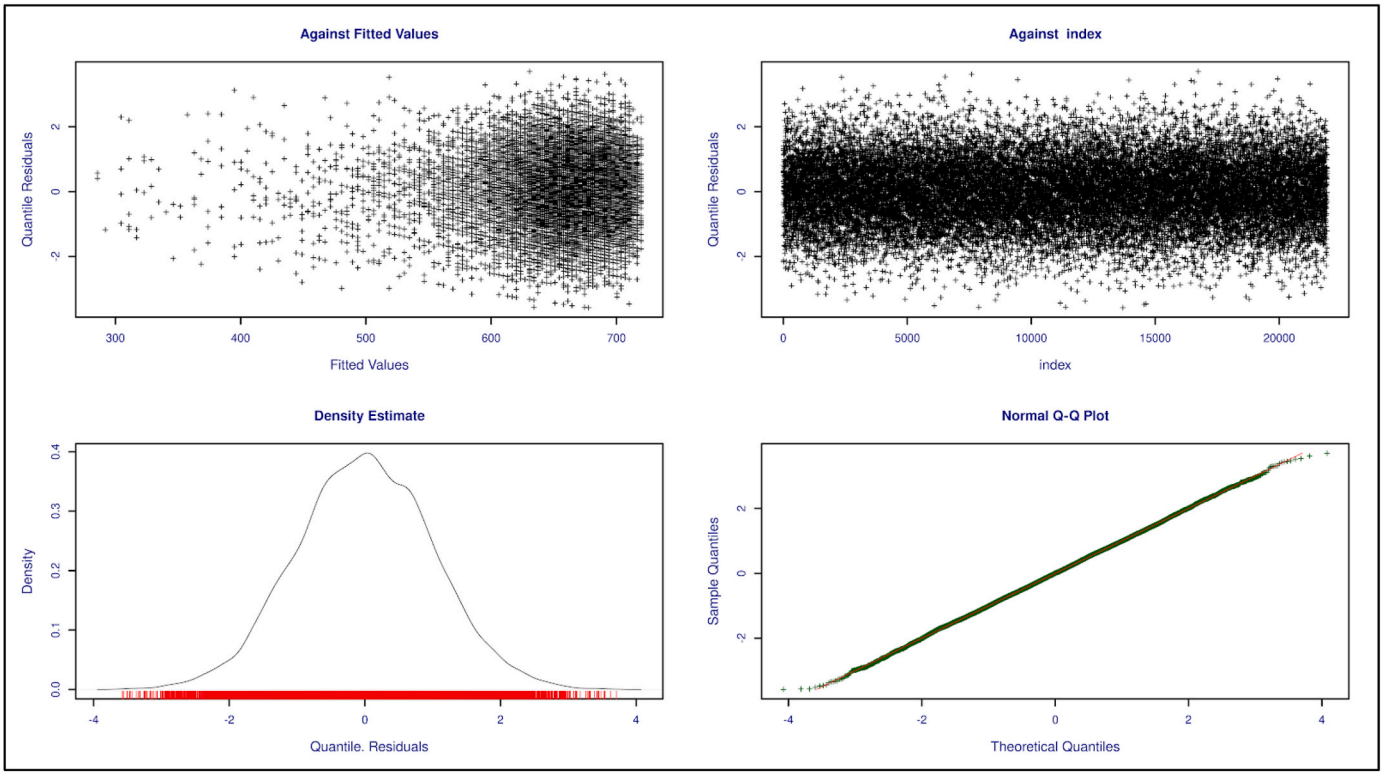

Fig. 2. Male fetuses to nulliparous mothers placenta weight centiles goodness of fit plots.

contrast to normal vasodialtion in preeclamptic mothers of female fetuses [8].

The limitations of this study are those that are inherent in using retrospective cross-sectional data for growth curves. The centiles were also only calculated on singleton fetuses and as such are not applicable to pregnancies of multiplicity where the increased demand on the placenta may have different implications on the influence of sex and or parity. Cross-sectional designs only allow for the individual measure of placental size or evaluation of the feto-placental weight ratio at specific gestational time points and should not be used to assess growth trajectory [28]. Curves based on a normal healthy population would be ideal to create standards that reflect the optimal placental weight rather than references based on the general population. However, the physical measurement of a placenta can only be done in the context of birth, signifying the end of placental growth. Any birth prior to 37 weeks cannot be considered a "normal" reference as there may be biological anomalies responsible for the preterm birth, with maternal vascular malperfusion lesions alone being present in more than 47% of preterm birth placentas [29]. It is possible that the use of the MoBa study cohort could be subject to selection bias. Thompson et al. had previously created centiles for placenta weight but stratified for only sex using the Norweigian Medical Birth Registry [11] and comparison between these centiles and our results show good congruence particularly for the MoBa multiparous mothers (Supplementary Fig. 20). Where they do differ is in the smoothness of our centile curves compared to those produced by Thompson et al.

The easier adaptation of the maternal vascular system to the subsequent pregnancies ensures adequate perfusion of the placenta and fetus. This critical difference between nulliparous and multiparous pregnancies results in larger placentas earlier in pregnancy. The importance of parity on placenta growth has largely been overlooked in the development of reference curves. However, while the influence of parity results in larger differences than does fetal sex, both have vital implications on a healthy placenta and should be considered in unison. Similar to the only other two studies, we have illustrated that parity has a great influence on the well-being of the placenta and its growth. These adjustments improve the accuracy and utility of the centiles, specifically in a Scandinavian cohort. However, further work is greatly needed to develop methods that can accurately map longitudinal placental measures to assess placental growth and trajectory throughout pregnancy.

Declaration of competing interest

The authors declare that they have no conflicts of interests.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.placenta.2021.10.011.

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Author contributions

Conceptualization, C.F., B.J, P.R.N.; formal analysis, C.F.; writing—original draft preparation, C.F., P.S.-N and B.J.; writing—review and editing, C.F., P.S.-N., M.V., O.H., D.M., S.J., B.J. and P.R.N. All

authors contributed to the interpretation of results and critically reviewed the manuscript. All authors have read and agreed to the published version of the manuscript.

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