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Inter-pregnancy interval and placental weight. A population based follow-up study in Norway

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ABSTRACT

Introduction: We studied changes in placental weight from the first to the second delivery according to length of the inter-pregnancy interval.
Methods: We followed all women in Norway from their first to their second successive singleton pregnancy during the years 1999–2019, a total of 271 184 women. We used data from the Medical Birth Registry of Norway and studied changes in placental weight (in grams (g)) according to the length of the inter-pregnancy. Adjustments were made for year and maternal age at first delivery, changes in the prevalence of maternal diseases (hypertension and diabetes), and a new father to the second pregnancy.
Results: Mean placental weight increased from 655 g at the first delivery to 680 g at the second. The adjusted increase in placental weight was highest at inter-pregnancy intervals <6 months; 38.2 g (95 % CI 33.0g–43.4 g) versus 23.2 g (95 % CI 18.8g–27.7 g) at inter-pregnancy interval 6–17 months. At inter-pregnancy intervals ≥18 months, placental weight remained higher than at the first delivery, but was non-different from inter-pregnancy intervals 6–17 months. Also, after additional adjustment for daily smoking and body mass index in sub-samples, we found the highest increase in placental weight at the shortest inter-pregnancy interval. We estimated no difference in gestational age at delivery or placental to birthweight ratio according to inter-pregnancy interval.
Discussion: Placental weight increased from the first to the second pregnancy, and the increase was most pronounced at short inter-pregnancy intervals. The biological causes and implications of such findings remain to be studied.

1. Introduction

A well-functioning placenta is a prerequisite for fetal growth, and it is known that birthweight is higher at the second delivery compared to the first [1,2]. Such increase in birthweight may suggest that placental function is better in the second pregnancy. An improved placental function in the second pregnancy is supported by the reduced risk of preeclampsia and stillbirth in the second pregnancy [3,4]. These pregnancy complications are closely related to impaired placental function and with low placental weight [5–9].

Although, a second pregnancy reduces the overall risk of low birthweight and other adverse pregnancy outcomes, a short inter-pregnancy interval has been associated with increased risk of low birthweight [10–16]. One possible explanation for the low birthweight at short inter-pregnancy intervals in previous studies could be that women with low birthweight infants also have a short inter-pregnancy interval. In follow-up studies of women with successive pregnancies, the increased risks at short interpregnancy interval is questioned [17–21]. The risk of preeclampsia and the recurrence risk of stillbirth seem to be lowest at the shortest inter-pregnancy intervals [3,4,21]. Since some previous studies report that the risk of placental related pregnancy complications is reduced at short inter-pregnancy intervals, we hypothesize that placental weight increases from the first to the second pregnancy and that the increase is highest at short inter-pregnancy intervals.

We studied changes in placental weight from the first to the second delivery according to the length of the inter-pregnancy interval among all women in Norway with two successive singleton deliveries during the years 1999–2019. For comparison, we also studied changes in birthweight and in placental weight relative to birthweight (placental to birthweight ratio) according to the length of the inter-pregnancy

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interval.

2. Material and methods

Our study is a registry-based follow-up study. We followed all women in Norway from their first to their second successive singleton delivery during the years 1999–2019 by using data from the Medical Birth Registry of Norway [22]. This registry includes all births after 16 gestational weeks in Norway since 1967, and the reporting is compulsory for the midwife or the doctor who attend the delivery. By using the women's unique national person identification number, we could link successive deliveries. Placental weight at delivery has been reported to the Medical Birth Registry since 1999.

In total, 299 341 women had at least two singleton deliveries during the years 1999–2019 (Fig. 1, flow chart of the study sample). We excluded women who were pregnant after in vitro fertilization (n = 10 963) since placental weight and inter-pregnancy interval in these pregnancies may differ from pregnancies after natural conception [23]. We also excluded women without information about gestational age at delivery (n = 1116) or with gestational age <28 weeks at one or both deliveries (n = 2327). Among the remaining, women were excluded if they had no information about placental weight or had outlying values (<50 g (g) or >2500 g) (n = 13 751). Thus, we included 271 184 women with two singleton deliveries during the period 1999–2019.

2.1. Study factors

Our outcome measure was change from the first to the second delivery in placental weight, in grams (g). To calculate the change, we calculated placental weight in the second pregnancy minus placental weight in the first pregnancy for each woman. The placental weighing routines in Norway are as follows; the placenta with membranes, blood, and the umbilical cord attached is placed in a bowl immediately after the delivery. For reporting of placental weight, the weight of the bowl is subtracted from the total weight. Birthweight was measured within 2 h after birth. Placental to birthweight ratio was calculated as placental weight (in grams)/birthweight (in grams).

Inter-pregnancy interval was defined as the number of months from the first delivery until onset of the second pregnancy. The onset of the second pregnancy was estimated as the date of the second delivery minus gestational age at delivery (in days). The length of the inter-pregnancy interval was grouped as follows; <6 months, 6–17 months, 18–29 months, 30–41 months, 42–53 months, 54–65 months, and ≥66 months. In supplementary analyses, we divided the inter-pregnancy interval into six months intervals, 0–5, 6–11 months …, and 114–119 months.

Gestational age at delivery was based on fetal size at routine fetal ultrasound examination 17–19 weeks after the last menstrual period (for 98 % of the pregnancies) or from the first day of the last menstrual period (for 2 % of the pregnancies). The routine fetal ultrasound examinations and almost all deliveries took place at public hospitals. Antenatal and obstetric care in Norway is free of charge.

To adjust for possible changes in the composition of pregnant women or health care during our study period, we included in the data analyses the year of the first delivery (as a dichotomous variable for each year). The crude results are presented with fixed effect for year of the first delivery. As other potentially confounding factors, we included factors that have been associated with inter-pregnancy interval and/or placental weight; maternal age at the first delivery (<20, 20–24 …, and ≥35 years) [24], presence in the first pregnancy (yes/no) or the second pregnancy (yes/no) of any diabetes (type-1, type-2, or gestational diabetes) [25] or any hypertension (preeclampsia, gestational hypertension, or chronic hypertension) [7]. A new father to the second pregnancy [26] and the mother's country of birth (Norway, yes/no) [27] were also included as potentially confounding factors. In subsamples (supplementary analyses), we made adjustments for maternal daily smoking in the first trimester in the first or in the second pregnancy [28] and changes from the first to the second pregnancy in maternal pre-pregnancy body mass index (BMI) [29]. Information about maternal smoking in the first trimester was available in the Medical Birth Registry from 1999, but was missing for some women in either the first or the second pregnancy. Thus, we could include 202 942 women in the analyses. Information about pre-pregnancy BMI was available from 2008, was missing for many, and we could include 70 621 women in the analyses with additional adjustment for BMI.

2.2. Statistical analyses

We calculated mean placental weight and mean birthweight with standard deviations (SD) at the first and the second delivery. Thereafter, we estimated crude and adjusted changes in placental weight (in grams (g)) and placental to birthweight ratio from the first to the second delivery (with 95 % confidence interval (CI)) according to the length of the inter-pregnancy interval. We also estimated crude changes in gestational age at delivery from the first to the second delivery (in days) according to the length of the inter-pregnancy interval (supplementary analysis). Changes in placental weight and gestational age were estimated by linear regression analyses, applying STATA version 17.0.

3. Results

3.1. Descriptive statistics

Mean crude placental weight was 655 g (standard deviation (SD) 144 g) at the first delivery, and it was 680 g (SD 147 g) at the second delivery (Table 1). Mean inter-pregnancy interval was 27.1 months (SD 19.4 months) and mean maternal age at the first delivery was 27.0 years (SD 4.4 years). Mean gestational age was 279.6 days at the first delivery and 279.2 days at the second. The distributions of sample characteristics according to length of the inter-pregnancy interval are presented in Supplemental Table 1.

3.2. Regression analyses

The highest increase in placental weight was estimated at inter-pregnancy intervals <6 months, 43.2 g (95 % CI 39.1g–47.3 g) after adjustment for year of first delivery (Fig. 2, Supplemental Table 2). At inter-pregnancy interval 6–17 months, the increase in placental weight was 28.6 g (95 % CI 25.7g–31.6 g), and we estimated no difference in placental weight between inter-pregnancy intervals 6–17 months and the inter-pregnancy intervals beyond. Adjustments for potentially confounding factors attenuated the increase, but still the highest increase in placental weight was estimated at <6 months inter-pregnancy interval (38.2 g (95 % CI 33.0g–43.4 g) versus 23.2 g (95 % CI 18.8g–27.7 g) at inter-pregnancy interval 6–17 months Also, when we made the inter-pregnancy intervals shorter (six months intervals), the highest increase in placental weight was at <6 months inter-pregnancy interval, and we identified no trend in placental weight at inter-pregnancy intervals beyond 6 months (Supplemental Fig. 1, Supplemental Table 3).

After additional adjustment for smoking in the first or second pregnancy, the highest increase in placental weight at the shortest inter-pregnancy interval remained (<6 months; 37.3 g (95 % CI 31.3 g–43.4 g) versus 6–17 months; 21.5 g (95 % CI 16.3g–26.7 g) (Supplemental Fig. 2, Supplemental Table 4). Also, in the sub-sample with available information about BMI, we found similar results, however, the confidence intervals overlapped (<6 months; 37.9 g (95 % CI 25.7g–50.2 g) and 6–17 months; 23.2 (95 % CI 12.1–34.4)) (Supplemental Fig. 3, Supplemental Table 5). We repeated our main data analysis among women who delivered at gestational week 39–41 in both pregnancies (n = 154 357), and the highest increase in placental weight at <6 months inter-pregnancy interval remained (35.6 g; 95 % CI 28.6–42.6). However, the 95 % CI were wide and overlapped other

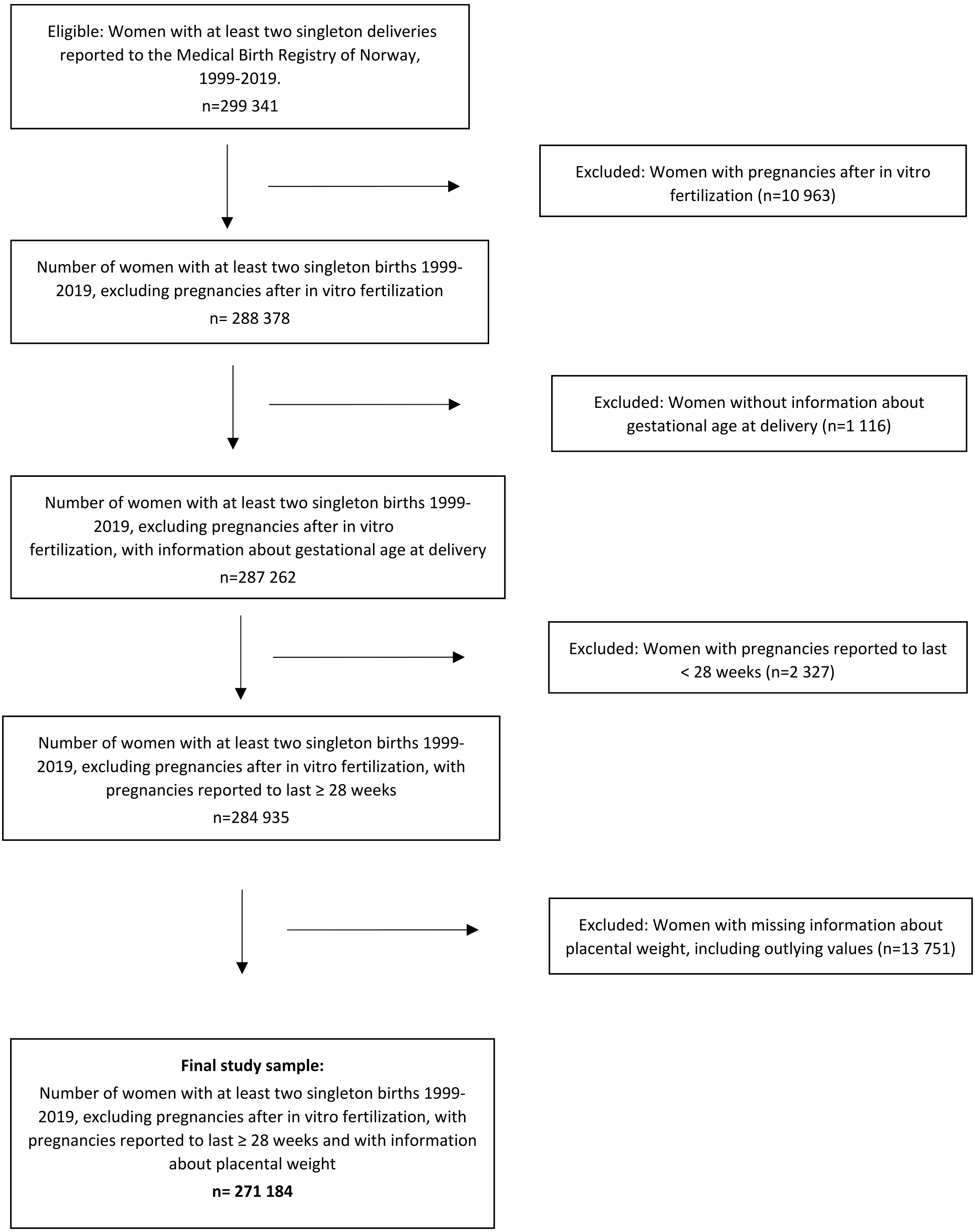

Fig. 1. Flow chart of the study sample.

Table 1
Characteristics of the study sample. All women in Norway with their first and second singleton delivery during the period 1999–2019 (n = 271 184).

Variable	First delivery	Second delivery
Mean (SD)		
Placental weight (grams)	655.1 (144.2)	680.2 (146.8)
Gestational age at delivery (days)	279.6 (12.4)	279.2 (10.6)
Inter-pregnancy interval (months)		27.1 (19.4)
Maternal age (years)	27.0 (4.4)	
Proportion (%)		
Mother's age:		
<20 years	4.4	
20–24 years	25.0	
25–29 years	42.2	
30–34 years	23.6	
≥35 years	4.8	
Diabetes[a]	2.0	3.1
Preeclampsia/hypertension[b]	7.1	3.6
Daily smoking during first trimester[c]	11.3	7.1
Maternal pre-pregnancy body mass index[d]	23.8	24.5
New father to second pregnancy		6.8
Mother not born in Norway	19.4	

[a] Includes type-1 diabetes, type-2 diabetes and gestational diabetes.
[b] Includes preeclampsia, gestational hypertension and chronic hypertension.
[c] Information about maternal smoking during first trimester was available for 202 942 women.
[d] Information about body mass index was available for 2008–2019 (n = 70 621).

inter-pregnancy intervals (Supplemental Fig. 4, Supplemental Table 6).

Mean birthweight increased from the first to the second delivery (mean increase 183 g) (Supplemental Table 7). Women with inter-pregnancy interval <6 months had the lowest mean birthweight at the first delivery, but the highest increase in birthweight to the second delivery (199 g). The relative increase in placental weight at inter-pregnancy interval <6 months was higher that the increase in birthweight. Thus, the estimated increase in placental to birthweight ratio was highest at inter-pregnancy intervals <6 months. The 95 % CI around the increase in placental to birthweight ratio were overlapping across all inter-pregnancy intervals (Fig. 3) (Supplemental Table 8).

We estimated no difference in the changes in gestational age from the first to the second delivery according to inter-pregnancy interval (Supplemental Fig. 5, Supplemental Table 9).

4. Discussion

4.1. Principal findings

In this follow-up study of 271 184 women, mean placental weight increased from the first to the second delivery, and the highest increase was at the shortest inter-pregnancy interval (<6 months).

4.2. Results in the context of what is known

We are aware of no previous studies about placental weight according to the length of the inter-pregnancy interval. Data that may be used for follow-up studies of placental weight across pregnancies are, to our knowledge, scarce. Mean placental weight at second deliveries has been reported higher than at first [30], and a small placenta has been associated with pregnancy complications at term [7–9]. A short inter-pregnancy interval may reduce the risk of placental related pregnancy complications such as stillbirth, preeclampsia and miscarriage [21,22,31].

Many previous studies, however, report that a short inter-pregnancy interval increases the risk of adverse pregnancy outcomes, such as low birthweight and preterm birth [11–16,32,33]. However, the relation of a

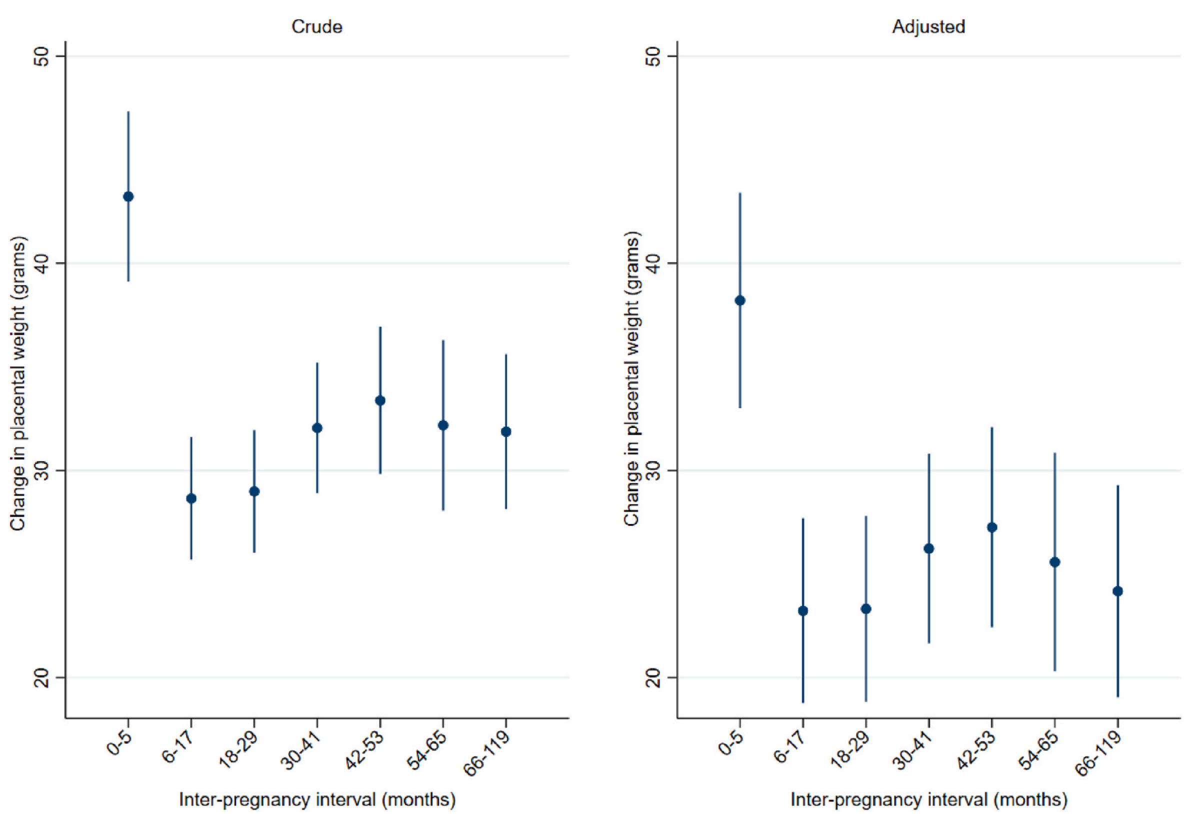

Fig. 2. Change in placental weight in grams (with 95 % confidence intervals) according to inter-pregnancy interval. All women with their first and second singleton delivery during the period 1999–2019 (n = 271 184). Note: Fixed effect for year of first delivery included in both analyses. Control variables: Mother's age at first delivery, diabetes in first and second pregnancy, hypertension in first and second pregnancy, new father to second pregnancy and whether mother is born abroad.

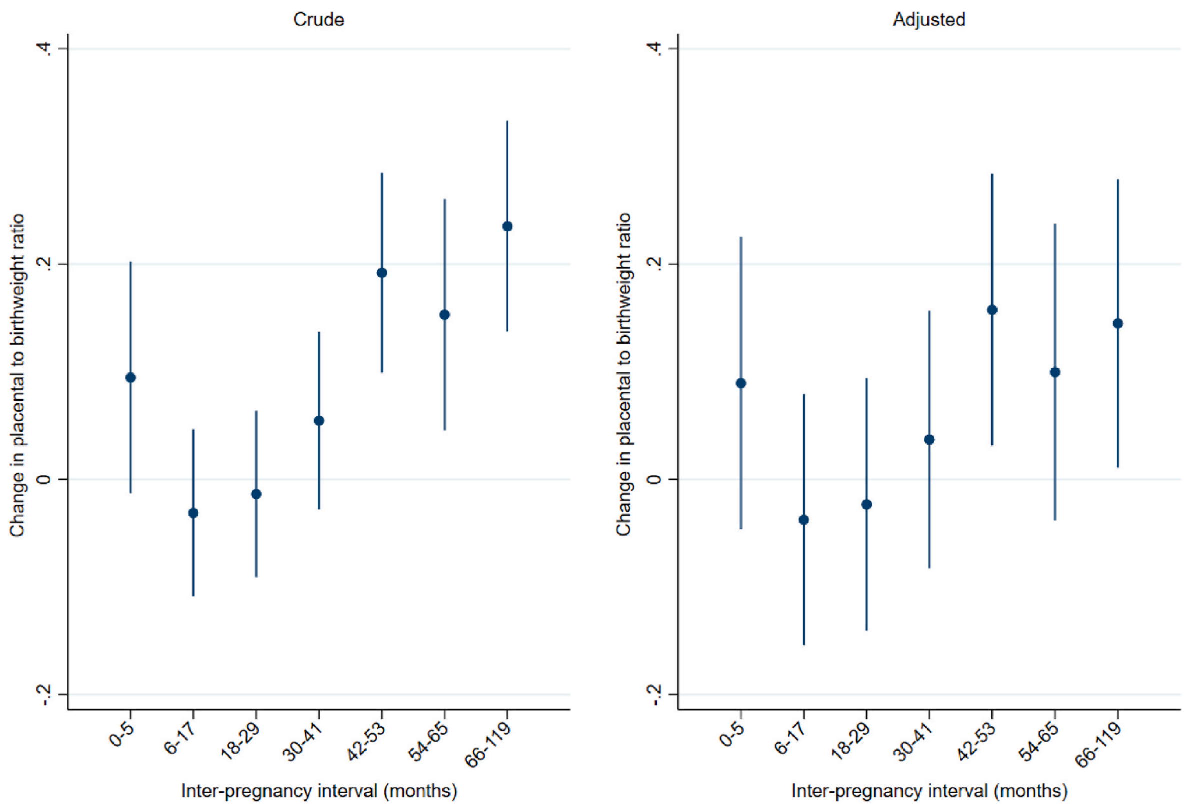

Fig. 3. Change in placental to birthweight ratio (with 95 % confidence intervals) according to inter-pregnancy interval. All women with their first and second singleton delivery during the period 1999–2019 (n = 271 184). Note: Fixed effect for year of first delivery included in both analyses. Control variables: Mother's age at first delivery, diabetes in first and second pregnancy, hypertension in first and second pregnancy, new father to second pregnancy and whether mother is born abroad.

short inter-pregnancy interval with adverse pregnancy outcomes is being questioned [20], and the relation of inter-pregnancy interval with adverse pregnancy outcomes may vary according to study design and between high and low income countries [34]. Low birthweight may indicate impaired intrauterine conditions for the offspring. In our study, women with inter-pregnancy interval <6 months had the lowest mean offspring birthweight at both deliveries compared to women with longer inter-pregnancy intervals. However, the highest increase in birthweight from the first to the second delivery was at inter-pregnancy intervals <6 months. Our findings therefore suggest that the low birthweight at short pregnancy intervals in many previous studies, could be a result of a selection to short inter-pregnancy intervals of women with low offspring birthweight and not a result of impaired intrauterine conditions.

4.3. Clinical implications - the meaning of the study

We found the highest increase in placental weight from the first to the second delivery at the shortest inter-pregnancy interval. Underlying factors that are linked to both short inter-pregnancy interval and high placental weight may explain our finding. High fecundity could be one such factor. Women with high fecundity may get pregnant shortly after a delivery. However it is not known whether high fecundity is associated high placental weight, and the higher placental weight in pregnancies after in vitro fertilization does not support such association [23].

The higher placental weight at second delivery may suggest that maternal conditions for placental growth improve from the first to the second pregnancy. Possibly, a maternal biological memory of being pregnant and of the interaction with a feto-placental unit exists. Such memory may be best shortly after a pervious pregnancy. It is known that a biological memory of immune responses exists [35]. The implantation of the blastocyst into the endometrium and the development of the placenta depends on a complex interaction between trophoblastic cells in the placenta and the endometrium in the uterus. Both immunological and angiogenic factors are involved [36]. Cells from the fetoplacental unit from a first pregnancy may be present in the woman after the pregnancy. Such fetal cells are biologically active, have stem cells characteristics, and may affect different maternal tissues [37,38]. It is conceivable that fetal cells from a previous pregnancy may enhance maternal responses to a new pregnancy and the interaction between the mother and the fetoplacental unit.

A pregnancy enhances large alterations in the maternal cardiovascular system [39–41], and these changes are essential for the provision of oxygen and nutrients to the fetoplacental unit. Possibly, the maternal cardiovascular alterations that take place in a pregnancy remain after the delivery or may be reactivated [39]. The potentials for such reactivation may weaken over time. The availability of oxygen and nutrients from the maternal circulation may be highest shortly after a previous pregnancy and thereby enhance placental growth.

The hypothesis of increased oxygen supply to the fetoplacental unit from pregnant women with short inter-pregnancy interval is supported by their lower risk of preeclampsia [3,21]. Preeclampsia is likely be caused by placental hypoxia and is closely linked to low levels of pro-angiogenic factors in the maternal circulation [42].

The relation of placental size with placental function remains largely unknown. However, it is conceivable that a larger placenta in a second pregnancy explains the reduced risk of placental related complications in a second pregnancy compared to the first [3,4,31]. In our study, we found the highest increase in birthweight at the shortest inter-pregnancy interval. This finding may suggest that placental function is best shortly after a previous pregnancy. Our findings give little reason to discourage a short interval between pregnancies.

4.4. Strengths and limitations

We used data from the Medical Birth Registry of Norway, and we aimed to include all women with two successive singleton deliveries at gestational week 28 or beyond in Norway during the years 1999–2019. Women without information about the main study factors were excluded (10 %). The exclusion was independent of the length of the inter-pregnancy interval (data not shown). Pregnancies lasting shorter than 12 weeks are not reportable to the Medical Birth Registry of Norway, and information about placental weight was lacking for a large proportion of women (78 %) with delivery prior to gestational week 28. Therefore, we could not study to what extend a pregnancy lasting shorter than 28 weeks, influences the inter-pregnancy interval, placental weight, or the association between these factors.

We followed individual women and studied changes in placental weight from the first to the second pregnancy. Such inter-individual approach reduces the risk of biases that may occur in cross-sectional studies if women with a predisposition for large or small placentas also have short inter-pregnancy interval. Nevertheless, we adjusted for factors that have been associated with placental weight and/or the interval between pregnancies such as maternal age, diabetes and smoking. Such adjustments attenuated the point estimated increase in placental weight, but the increase remained highest at inter-pregnancy intervals <6 months. Weight change between pregnancies is associated with placental weight [29], and women's BMI may be higher shortly after a delivery than years after. In supplemental analyses with adjustment for BMI, our findings remained. However, the confidence intervals were overlapping. Gestational age was similar at first and second delivery and across inter-pregnancy intervals and is therefore unlikely to have biased our results. Confounding may remain. Socioeconomic status may be related to placental weight and inter-pregnancy interval. Unfortunately, we had no information about education or income. It is difficult to conceive, however, that changes in individual socioeconomic status is most prominent among women with the shortest inter-pregnancy interval.

Our findings may not be generalizable to pregnant women across the world. Studies that may be used for reliable comparison of placental weight across populations are scarce [30,43]. Also, the availability and quality of health care may affect placental weight and the interval between pregnancies. The public antenatal and obstetric health care in Norway has high quality, is free of charge, and is used by almost all pregnant women [44]. Additionally, first trimester pregnancy termination may be legally performed on the woman's request, and pregnancy termination is free of charge.

5. Conclusions

In this follow-up study of all women in Norway with two singleton successive deliveries during the years 1999–2019, placental weight increased from the first to the second delivery, and the increase was highest at the shortest inter-pregnancy interval. The increase in placental size could possibly explain the reduced risk of some placental related pregnancy complications in a second pregnancy, particularly when the inter-pregnancy interval is short.

Authors' contribution

AE had the idea to the study and wrote the manuscript. JG and IS performed the data analyses contributed to the interpretation of the results and the writing of the manuscript. CH interpreted the results and wrote the manuscript.

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Details of ethical approval

This study was approved by the Regional Committee for Medical and Health Research Ethics, Norway (REK 20/15255-2). We used data from the Medical Birth Registry in Norway. The reporting by health personnel of births to the Medical Birth Registry in Norway is compulsory by law. Individual informed consent is not necessary for the reporting.

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Tweetable statement

Placental weight increases from the first to the second delivery, and the increase is most prominent if the inter-pregnancy interval is short.

Declaration of competing interest

The authors report no conflict of interest.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.placenta.2023.11.003.

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