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Interpregnancy weight changes and impact on pregnancy outcome in a cohort of women with a macrosomic first delivery: A Prospective Longitudinal Study.

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Title: Interpregnancy weight changes and impact on pregnancy outcome in a cohort of women with a macrosomic first delivery: A Prospective Longitudinal Study.

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Running Title: Interpregnancy weight gain and impact on pregnancy outcome

Abstract:

Objective:

To determine the median interpregnancy maternal weight change between first and second pregnancies, and second and third pregnancies and to assess the impact of this weight change on pregnancy outcome in a cohort of women with a macrosomic first delivery.

Study Design:

Prospective longitudinal study conducted over three pregnancies from 2007 to 2015.

Setting:

Tertiary referral maternity hospital, Dublin, Ireland

Participants:

Women were recruited if their first baby weighed over 4.0kg.

Methods:

The pregnancy outcomes in the second and third pregnancies were analysed separately. Data were also analysed for both interpregnancy intervals comparing outcomes for those who gained any weight, or more weight than the median, with those who did not.

Main Outcome Measures:

Recurrent fetal macrosomia ≥ 4.0kg

Gestational diabetes mellitus

Results:

There were 280 women who delivered a third baby between 2011 and 2015. There were no difference in pregnancy outcomes for the second pregnancy in women who gained interpregnancy weight compared with those who did not and those who gained more interpregnancy weight than the median compared with those who did not. There was a statistically significant increase in birthweight ≥ 4.0kg (54.0% vs. 39.6% p=0.03) in those women who gained any weight between the second and third pregnancies. In those women who gained more interpregnancy weight than the median (1.70kg) between a second and third pregnancy, there was a significant increase in the rate of gestational diabetes (6.5% vs 1.4%, p=0.03).

Conclusions:

This longitudinal study demonstrates that within this cohort, maternal interpregnancy weight change between a second and third pregnancy is associated with an increase in birthweight ≥ 4.0kg. Additionally a gain of more weight than the median (1.70kg) is associated with a higher rate of gestational diabetes.

Key words: Interpregnancy weight change
Body mass index
Fetal macrosomia
Gestational diabetes mellitus

Article Summary

Strengths and Limitations

- Maternal weight and height were measured at booking visit in each pregnancy <18 weeks gestation and BMI calculated accurately, rather than relying on maternal self-reporting.
- Uniform cohort: they delivered a first baby weight >4.0kg and they did not have GDM or hypertensive disorders in the first pregnancy.
- Data was prospectively collected by an investigator and accurately recorded into an anonymised computerised database.
- Longitudinal study, which has advantages over a cross-sectional study.
- A potential limitation of this study is that we do not have data on women who attended elsewhere for subsequent antenatal care.

Introduction:

Fetal macrosomia is a common obstetric problem, affecting up to 20% of babies born at term (1, 2). The incidence varies according to the birthweight cut-offs employed, as it is varyingly defined as an absolute birthweight greater than 4000 g, 4500 g, or as a customised birth weight centile of greater than the 90th, 95th or 97th percentile for the infant's gestational age (3). It is associated with adverse obstetric maternal outcomes and neonatal outcomes, such as hypoglycaemia, hypomagnesaemia and hyperbilirubinaemia (4-6). Furthermore, infants with increased weight and body mass index (BMI) are more likely to be obese in childhood (7), and this is contributing to the burden of obesity on global health (3). Women with a history of birth of a macrosomic infant are at significantly increased risk of delivering another macrosomic infant in a subsequent pregnancy (8), and the risk increases further with a history of two macrosomic infants (9). Maternal weight gain during pregnancy influences fetal birthweight (10), and excessive gestational weight gain is strongly associated with fetal macrosomia (11). Interventions to limit gestational weight gain are, however, limited at best, perhaps due to perceived concerns regarding dietary and lifestyle changes during the prenatal period (12).

Less attention has been traditionally focused on weight changes, and weight gain in particular, during the interval between pregnancies. Interpregnancy weight gain has, however, been associated with gestational hypertensive disease, gestational diabetes (GDM), caesarean section (CS), fetal macrosomia and even stillbirth (13-16). The postpartum and interval pregnancy time period therefore may represent a specific opportunity for targeted public health education, in women from every BMI category to

prevent movement into a higher BMI category (17). To date, there are paucity of published longitudinal data on interpregnancy weight changes and the impact on both maternal and neonatal outcomes.

The objective of this longitudinal study was to determine the median interpregnancy maternal weight change between first and second pregnancies, and second and third pregnancies and to assess the impact of this weight change on pregnancy outcome in a cohort of women with a macrosomic first delivery.

Methods:

This is a prospective longitudinal study over three pregnancies. Women were initially recruited to the ROLO study (Randomised cOntrol trial of LOw glycaemic index diet versus no dietary intervention to prevent recurrence of fetal macrosomia) if their first baby weighed over 4.0kg (8). Recruitment to the randomised trial, with institutional ethical approval and maternal written consent, commenced in January 2007 and completed in January 2011. 800 secundigravida women without diabetes, who had previously given birth to a macrosomic baby (> 4.0kg) and were therefore at increased risk of delivering another macrosomic infant (9), were randomised to receive either low glycaemic index (GI) dietary advice or usual antenatal care. Detailed methodology and results of the ROLO study have previously been published (8, 18). In brief; the low GI diet did not impact on birthweight, but maternal benefits were noted in terms of less gestational weight gain (12.2 Kg vs. 13.7Kg, $p< 0.05$) and less glucose intolerance (21% vs. 28%, $p<0.05$). Low GI dietary advice was given at week 14 of pregnancy and the women in the intervention group were found to have a significantly reduced glycaemic index and glycaemic load following the intervention (8).

Mothers were then followed prospectively and data collated and anonymised on 280 women who delivered two further babies up to 2015. Weight and height were measured accurately at first presentation prior to 18 weeks gestation in each pregnancy and BMI calculated. Relevant descriptive statistics were obtained for the study population.

The pregnancy outcomes in the second and third pregnancies were analysed separately with respect to the previous interpregnancy period, using absolute weight change. Data were also analysed for both interpregnancy intervals comparing outcomes for those who gained any weight, or those who gained more weight than the median with those who did not, which may be a more convenient definition for clinical practice. The pregnancy outcomes analysed were CS, GDM, recurrent fetal macrosomia, gestational hypertensive disease, neonatal intensive care unit (NICU) admission and stillbirth. We used the Mann-Whitney-U test to evaluate differences in continuous variables between the groups or over time and χ^2 tests to compare categorical variables between groups. We set statistical significance at $P<0.05$ and used SPSS version 23.0 for statistical analysis.

Results:

Of the initial 800 women recruited to the ROLO study, 280 (35.0%) women delivered a third baby between 2011 and 2015. Of these, the median maternal weight in the first pregnancy was 68.8kg (IQR 16.5) and the median BMI was 24.9kg/m^2 (IQR 4.7). In total, 11.4% (n=32) of the cohort were obese in the first trimester of the first pregnancy. Table 1 details the demographic data for the cohort in the first trimester of the first, second and third pregnancies respectively.

Overall, 72.9% (n=204) gained weight between the first and second pregnancy within a median interpregnancy interval of 24 months (IQR 12.0) and the overall median weight change was 2.60kg (IQR 3.5). 67.5% (n=189) gained weight between the second and third pregnancy within a median interpregnancy interval of 36.0 months (IQR 24.0), and the overall median weight change was 1.70kg (IQR 5.3). This resulted in a median weight gain from first to third pregnancy of 4.30kg (IQR 7.5). Overall the rate of obesity rose from 11.4% in first pregnancy to 22.1% by the beginning of the third pregnancy.

There were no difference in pregnancy outcomes for the second pregnancy (gestational hypertensive disease, GDM, CS , recurrent fetal macrosomia ≥ 4kg, NICU admission and stillbirth) in women who gained interpregnancy weight compared with those who did not and those who gained more interpregnancy weight than the median compared with those who did not.

There was a statistically significant increase in birthweights ≥ 4.0kg (54.0% vs. 39.6% p=0.03) in those women who gained weight between the second and third pregnancies. In those women who gained more interpregnancy weight than the median (1.70kg) between a second and third pregnancy, there was a significant increase in the rate of gestational diabetes (6.5% vs. 1.4%, p=0.03). There were no differences in gestational hypertensive disease, CS, NICU admission and stillbirth (Table 3).

To examine the effect of cumulative weight gain over both interpregnancy intervals, and to control for the effect of maternal age and BMI less than 18 weeks gestation in the index pregnancy on the above results, logistic regression models to predict a birthweight ≥ 4.0kg were run. Weight gain between the first and second, second and

third and overall between first and third pregnancies had broadly similar effects, with a 2-3% higher odds of a high birthweight per kilogram gain, which increased to 3-5% when adjusting for maternal age and BMI. Statistical significance was marginal, but present for weight gain in the earlier interval and between first and third pregnancies.

Discussion:

Main Findings

This longitudinal study found that women who delivered a macrosomic infant ≥4.0kg in their first pregnancy without gestational diabetes gained a median of 2.60kg between a first and second pregnancy and a median of 1.70kg between a second and third pregnancy resulting in a median 4.30kg weight gain from first to third pregnancy. This resulted in increase in obesity rates from 11.4% in first pregnancy to 22.1% in third pregnancy, highlighting the central role pregnancy has in weight gain across the life course. The interpregnancy weight gain between first and second pregnancies did not appear to impact on pregnancy outcome, however interpregnancy weight gain between second and third pregnancies was associated with an increased rate of recurrent fetal macrosomia ≥4.0kg. Additionally those with a weight gain of more than the median (≥1.70kg) between second and third pregnancies was associated with increased incidence of GDM.

Interpretation

One possible explanation for the lack of associations in second pregnancy may arise due to the Hawthorne effect of trial participation in both the intervention and control arms. Another more likely hypothesis could be that weight gain may be cumulative. The median weights at booking visit in the first, second and third pregnancies were 68.8kg,

71.3kg and 73.1kg respectively. Is weight gain cumulative so that it is only over a certain level that effects on birthweight and GDM are noted? There are a paucity of longitudinal studies on postpartum weight changes, because these studies are challenging to conduct (19). This longitudinal study adds to the evidence that interpregnancy weight gain causes GDM and macrosomic babies. Many studies relating to interpregnancy weight changes are cross sectional and retrospective in nature. Furthermore, many of these studies use self-reported maternal weight, which can be unreliable and leads to BMI miscategorization (20). High postpartum weight retention is an important contributor to long-term maternal obesity, which has detrimental effects on long-term maternal health (21).

Strengths and Limitations in relation to other studies

Bogaerts et al. found that in a population of 7,897 women in Belgium, there was an increase rate of GDM (aOR 2.25, 95% CI 1.33-3.78; P=0.002) in those who had interpregnancy weight retention of 2 or more BMI units. However, this study used self-reported prepregnancy weight and no prior information on hypertension and GDM available (15). A large Swedish retrospective epidemiological study of 151,025 women who had their first two consecutive births between 1992 and 2001 found that those who gained 3 or more BMI units between pregnancies compared with those women whose BMI changed between -1.0 and 0.9 units had an adjusted odds ratio of GDM of 2.09 (1.68-2.61) (13). Wallace et al. (22) conducted a retrospective cohort study of 12,740 women in Aberdeen, Scotland who delivered their first and second children between 1986 and 2007. Weight gain of greater than three BMI units was associated with an increase in large for gestational age infants. Jain et al. (23) analysed a population based historical cohort of 10,444 obese women in Missouri who delivered their first infant between 1998-2005. Interpregnancy weight gain was associated with

an increased risk of a LGA infant (aOR 1.37; 95% CI, 1.21-1.54). These studies are retrospective. Our study is a prospective longitudinal illustrating that interpregnancy weight gain is associated with recurrent fetal macrosomia in a unique population of women who delivered a macrosomic baby ≥ 4.0 kg in their index pregnancy, and that interpregnancy weight gain of greater than the median is associated with an increased rate of GDM.

The interpregnancy interval is an important time for diet and lifestyle intervention in women who have delivered a macrosomic infant in their first pregnancy in the prevention of recurrent macrosomia and the development of GDM.

Strengths and Limitations

This longitudinal study has strengths. Maternal weight and height were measured at booking visit in each pregnancy <18 weeks gestation and BMI calculated accurately, rather than relying on maternal self-reporting. Furthermore, this cohort of women was uniform in that they delivered a first baby weight >4.0kg and they did not have GDM or hypertensive disorders in the first pregnancy. Data was prospectively collected by an investigator and accurately recorded into an anonymised computerised database. Finally, this longitudinal study has advantages over a cross-sectional study.

A potential limitation of this study is that we do not have data on women who attended elsewhere for subsequent antenatal care. Another potential limitation is that the interpregnancy interval varied between subjects within this study. Finally, this study applies to women who delivered a first baby >4kg, which applies to approximately 15% of our overall primiparous population.

Conclusions:

This longitudinal study demonstrates that within this cohort maternal interpregnancy weight change between a second and third pregnancy is associated with an increase in birthweight ≥ 4.0kg. Additionally a gain of more weight than the median (1.70kg) is associated with a higher rate of gestational diabetes. It is important to identify ways for women to maintain a normal weight and BMI throughout her life, particularly between pregnancies. Obstetricians should consider postnatal advice on interval pregnancy weight gain in order to reduce rates of macrosomia and gestational diabetes in future pregnancy in at risk women.

Acknowledgments

Nil of note

Contribution to Authorship

FMMcA conceived and designed the study. JW contributed to the study design and manuscript preparation. DAC performed the analysis and wrote the manuscript. RS performed analysis. All of the authors reviewed and revised the final version of the manuscript. FMMcA is the guarantor.

Ethical Approval

Not applicable

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This research received no specific grant from any funding agency in the public, commercial or not-for-profit sectors.

Competing Interests

We have read and understood BMJ policy on declaration of interests and declare that we have no competing interests.

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Table 1: Demographics of the cohort at in the first trimester of the first, second and third pregnancies respectively (n=280)

	Pregnancy 1	Pregnancy 2	Pregnancy 3
Maternal Age (years)	29.0 (8.1)	31.8 (5.5)	34.8 (5.8)
Maternal Weight (kg)	68.8 (16.5)	71.4 (17.5)	73.1 (19.4)
BMI (kg/m^2)	24.9 (4.7)	25.7 (5.4)	26.0 (5.7)
Birthweight (kg)	4.2 (0.26)	4.1 (0.61)	4.0 (0.69)
Gestational Age (Days)	288 (10.0)	283 (11.0)	280 (13.8)
Obese ($\geq 30kg/m^2$)	11.4% (n=32)	20.0% (n=56)	22.1% (n=62)

All values are median with interquartile ranges in hypotheses, except for obesity (demonstrated in absolute numbers and percentages). Maternal weight and body mass index (BMI) were calculated at ≤ 18 weeks gestation.

Table 2. Effect of weight gain on odds of birthweight ≥4kg unadjusted and adjusted for maternal age and BMI calculated at less than 18 weeks gestation in the index pregnancy

	Unadjusted			Adjusted for maternal age and BMI		
	OR	95% CI	p-value	OR	95% CI	p-value
Weight gain from pregnancy 1 to 2	1.03	0.99, 1.07	0.169	1.05	1.01, 1.10	0.024
Weight gain from pregnancy 2 to 3	1.02	0.98, 1.06	0.243	1.03	0.99, 1.08	0.107
Weight gain from pregnancy 1 to 3	1.03	1.00, 1.06	0.093	1.04	1.01, 1.08	0.013

Table 3:

Pregnancy outcomes for the third pregnancy based on those who gained inter-pregnancy weight compared with those who did not and those who gained more inter-pregnancy weight than the median compared with those who did not.

	Gained interpregnancy weight n=189	**Did not gain interpregnancy weight n=91**	**P value**
CS overall	41 (21.7%)	21 (23.1%)	NS
GDM	9 (4.8%)	2 (2.2%)	NS
BW ≥4kg	102 (54.0%)	36 (39.6%)	P=0.03
Hypertensive Disease	5 (2.6%)	2 (2.2%)	NS
NICU	4 (2.1%)	2 (2.2%)	NS
Stillbirth	1 (0.5%)	1 (1.1%)	NS
	Gained > 1.70kg inter-pregnancy weight (n=139)	**Gained ≤ 1.70kg inter-pregnancy weight (n=141)**	**P value**
CS overall	28 (20.1%)	34 (24.1%)	NS
GDM	9 (6.5%)	2 (1.4%)	0.03
BW ≥4kg	75 (54.0%)	63 (44.7%)	NS
Hypertensive Disease	4 (2.9%)	3 (2.1%)	NS
NICU	4 (2.9%)	2 (1.4%)	NS
Stillbirth	0 (0%)	2 (1.4%)	NS

STROBE 2007 (v4) Statement—Checklist of items that should be included in reports of *cross-sectional studies*

Section/Topic	Item #	Recommendation	Reported on page #
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	2
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	3
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	5
Objectives	3	State specific objectives, including any prespecified hypotheses	6
Methods			
Study design	4	Present key elements of study design early in the paper	6
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	7
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants	6
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	7
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	7
Bias	9	Describe any efforts to address potential sources of bias	*N/A*
Study size	10	Explain how the study size was arrived at	
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	7
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	7
		(*b*) Describe any methods used to examine subgroups and interactions	N/A
		(*c*) Explain how missing data were addressed	N/A
		(*d*) If applicable, describe analytical methods taking account of sampling strategy	N/A
		(*e*) Describe any sensitivity analyses	N/A
Results			

Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	7
		(b) Give reasons for non-participation at each stage	N/A
		(c) Consider use of a flow diagram	N/A
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	7
		(b) Indicate number of participants with missing data for each variable of interest	N/A
Outcome data	15*	Report numbers of outcome events or summary measures	8
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	
		(*b*) Report category boundaries when continuous variables were categorized	8-9
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	N/A
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	N/A
Discussion			
Key results	18	Summarise key results with reference to study objectives	9
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	10-11
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	12
Generalisability	21	Discuss the generalisability (external validity) of the study results	12
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	N/A

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.

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Study Design:

Prospective longitudinal study conducted over three pregnancies from 2007 to 2015.

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Tertiary referral maternity hospital, Dublin, Ireland

Participants:

Women were recruited if their first baby weighed over 4.0kg.

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The pregnancy outcomes in the second and third pregnancies were analysed separately. Data were also analysed for both interpregnancy intervals comparing outcomes for those who gained any weight, or more weight than the median, with those who did not.

Main Outcome Measures:

Recurrent fetal macrosomia ≥ 4.0kg

Gestational diabetes mellitus

Results:

There were 280 women who delivered a third baby between 2011 and 2015. There were no difference in pregnancy outcomes for the second pregnancy in women who gained interpregnancy weight compared with those who did not and those who gained more interpregnancy weight than the median compared with those who did not. There was a statistically significant increase in birthweight ≥ 4.0kg (54.0% vs. 39.6% p=0.03) in those women who gained any weight between the second and third pregnancies. In those women who gained more interpregnancy weight than the median (1.70kg) between a second and third pregnancy, there was a significant increase in the rate of gestational diabetes (6.5% vs 1.4%, p=0.03).

Conclusions:

This longitudinal study demonstrates that within this cohort, maternal interpregnancy weight change between a second and third pregnancy is associated with an increase in birthweight ≥ 4.0kg. Additionally a gain of more weight than the median (1.70kg) is associated with a higher rate of gestational diabetes.

Key words: Interpregnancy weight change
Body mass index
Fetal macrosomia
Gestational diabetes mellitus

Article Summary

Strengths and Limitations

- Maternal weight and height were measured at booking visit in each pregnancy <18 weeks gestation and BMI calculated accurately, rather than relying on maternal self-reporting.
- Uniform cohort: they delivered a first baby weight >4.0kg and they did not have GDM or hypertensive disorders in the first pregnancy.
- Data was prospectively collected by an investigator and accurately recorded into an anonymised computerised database.
- Longitudinal study, which has advantages over a cross-sectional study.
- A potential limitation of this study is that we do not have data on women who attended elsewhere for subsequent antenatal care.

Data Sharing Statement

There is no additional unpublished data from this study. All co-authors can access this data. Anonymous data can be obtained by contacting the corresponding author.

Introduction:

Fetal macrosomia is a common obstetric problem, affecting up to 20% of babies born at term (1, 2). The incidence varies according to the birthweight cut-offs employed, as it is varyingly defined as an absolute birthweight greater than 4000 g, 4500 g, or as a customised birth weight centile of greater than the 90th, 95th or 97th percentile for the infant's gestational age (3). It is associated with adverse obstetric maternal outcomes and neonatal outcomes, such as hypoglycaemia, hypomagnesaemia and hyperbilirubinaemia (4-6). Furthermore, infants with increased weight and body mass index (BMI) are more likely to be obese in childhood (7), and this is contributing to the burden of obesity on global health (3). Women with a history of birth of a macrosomic infant are at significantly increased risk of delivering another macrosomic infant in a subsequent pregnancy (8), and the risk increases further with a history of two macrosomic infants (9). Maternal weight gain during pregnancy influences fetal birthweight (10), and excessive gestational weight gain is strongly associated with fetal macrosomia (11). Interventions to limit gestational weight gain are, however, limited at best, perhaps due to perceived concerns regarding dietary and lifestyle changes during the prenatal period (12).

Less attention has been traditionally focused on weight changes, and weight gain in particular, during the interval between pregnancies. Interpregnancy weight gain has, however, been associated with gestational hypertensive disease, gestational diabetes (GDM), caesarean section (CS), fetal macrosomia and even stillbirth (13-16). The postpartum and interval pregnancy time period therefore may represent a specific opportunity for targeted public health education, in women from every BMI category to

prevent movement into a higher BMI category (17). To date, there are paucity of published longitudinal data on interpregnancy weight changes and the impact on both maternal and neonatal outcomes.

The objective of this longitudinal study was to determine the median interpregnancy maternal weight change between first and second pregnancies, and second and third pregnancies and to assess the impact of this weight change on pregnancy outcome in a cohort of women with a macrosomic first delivery.

Methods:

This is a prospective longitudinal study over three pregnancies. Women were initially recruited to the ROLO study (Randomised cOntrol trial of LOw glycaemic index diet versus no dietary intervention to prevent recurrence of fetal macrosomia) if their first baby weighed over 4.0kg (8). Recruitment to the randomised trial, with institutional ethical approval and maternal written consent, commenced in January 2007 and completed in January 2011. 800 secundigravida women without diabetes, who had previously given birth to a macrosomic baby (> 4.0kg) and were therefore at increased risk of delivering another macrosomic infant (9), were randomised to receive either low glycaemic index (GI) dietary advice or usual antenatal care. Detailed methodology and results of the ROLO study have previously been published (8, 18). In brief; the low GI diet did not impact on birthweight, but maternal benefits were noted in terms of less gestational weight gain (12.2 Kg vs. 13.7Kg, $p< 0.05$) and less glucose intolerance (21% vs. 28%, $p<0.05$). Low GI dietary advice was given at week 14 of pregnancy and the women in the intervention group were found to have a significantly reduced glycaemic index and glycaemic load following the intervention (8).

Mothers were then followed prospectively and data collated and anonymised on 280 women who delivered two further babies up to 2015. Weight and height were measured accurately at first presentation prior to 18 weeks gestation in each pregnancy and BMI calculated. Relevant descriptive statistics were obtained for the study population.

The pregnancy outcomes in the second and third pregnancies were analysed separately with respect to the previous interpregnancy period, using absolute weight change. Data were also analysed for both interpregnancy intervals comparing outcomes for those who gained any weight, or those who gained more weight than the median with those who did not, which may be a more convenient definition for clinical practice. The pregnancy outcomes analysed were CS, GDM, recurrent fetal macrosomia, gestational hypertensive disease, neonatal intensive care unit (NICU) admission and stillbirth. We used the Mann-Whitney-U test to evaluate differences in continuous variables between the groups or over time and χ^2 tests to compare categorical variables between groups. We set statistical significance at $P<0.05$ and used SPSS version 23.0 for statistical analysis.

Results:

Of the initial 800 women recruited to the ROLO study, 280 (35.0%) women delivered a third baby between 2011 and 2015. Of these, the median maternal weight in the first pregnancy was 68.8kg (IQR 62.0,78.5) and the median BMI was 24.9kg/m^2 (IQR 22.7,27.3). In total, 11.4% (n=32) of the cohort were obese in the first trimester of the first pregnancy. Table 1 details the demographic data for the cohort in the first trimester of the first, second and third pregnancies respectively.

Overall, 72.9% (n=204) gained weight between the first and second pregnancy within a median interpregnancy interval of 24 months (IQR 23,35) and the overall median weight change was 2.60kg (IQR -0.28,3.28). 67.5% (n=189) gained weight between the second and third pregnancy within a median interpregnancy interval of 36.0 months (IQR 24,48), and the overall median weight change was 1.70kg (IQR -0.68,4.58). This resulted in a median weight gain from first to third pregnancy of 4.30kg (IQR 0.3,7.8). Overall the rate of obesity rose from 11.4% in first pregnancy to 22.1% by the beginning of the third pregnancy.

There were no difference in pregnancy outcomes for the second pregnancy (gestational hypertensive disease, GDM, CS , recurrent fetal macrosomia ≥ 4kg, NICU admission and stillbirth) in women who gained interpregnancy weight compared with those who did not and those who gained more interpregnancy weight than the median compared with those who did not.

There was a statistically significant increase in birthweights ≥ 4.0kg (54.0% vs. 39.6% p=0.03) in those women who gained weight between the second and third pregnancies. In those women who gained more interpregnancy weight than the median (1.70kg) between a second and third pregnancy, there was a significant increase in the rate of gestational diabetes (6.5% vs. 1.4%, p=0.03). There were no differences in gestational hypertensive disease, CS, NICU admission and stillbirth (Table 2).

To examine the effect of cumulative weight gain over both interpregnancy intervals, and to control for the effect of maternal age and BMI less than 18 weeks gestation in the index pregnancy on the above results, logistic regression models to predict a

birthweight ≥ 4.0kg were run. Weight gain between the first and second, second and third and overall between first and third pregnancies had broadly similar effects, with a 2-3% higher odds of a high birthweight per kilogram gain, which increased to 3-5% when adjusting for maternal age and BMI. Statistical significance was marginal, but present for weight gain in the earlier interval and between first and third pregnancies (Table 3).

Discussion:

Main Findings

This longitudinal study found that women who delivered a macrosomic infant ≥4.0kg in their first pregnancy without gestational diabetes gained a median of 2.60kg between a first and second pregnancy and a median of 1.70kg between a second and third pregnancy resulting in a median 4.30kg weight gain from first to third pregnancy. This resulted in increase in obesity rates from 11.4% in first pregnancy to 22.1% in third pregnancy, highlighting the central role pregnancy has in weight gain across the life course. The interpregnancy weight gain between first and second pregnancies did not appear to impact on pregnancy outcome, however interpregnancy weight gain between second and third pregnancies was associated with an increased rate of recurrent fetal macrosomia ≥4.0kg. For each kilogram increase in interpregnancy weight, the odds of giving birth to an infant of ≥4.0kg increased. Additionally those with a weight gain of more than the median (≥1.70kg) between second and third pregnancies was associated with increased incidence of GDM.

Interpretation

One possible explanation for the lack of associations in second pregnancy may arise due to the Hawthorne effect of trial participation in both the intervention and control arms. Another more likely hypothesis could be that weight gain may be cumulative. The median weights at booking visit in the first, second and third pregnancies were 68.8kg, 71.3kg and 73.1kg respectively. Is weight gain cumulative so that it is only over a certain level that effects on birthweight and GDM are noted? There are a paucity of longitudinal studies on postpartum weight changes, because these studies are challenging to conduct (19). This longitudinal study adds to the evidence that interpregnancy weight gain causes GDM and macrosomic babies. Many studies relating to interpregnancy weight changes are cross sectional and retrospective in nature. Furthermore, many of these studies use self-reported maternal weight, which can be unreliable and leads to BMI miscategorization (20). High postpartum weight retention is an important contributor to long-term maternal obesity, which has detrimental effects on long-term maternal health (21).

Strengths and Limitations in relation to other studies

Bogaerts et al. found that in a population of 7,897 women in Belgium, there was an increase rate of GDM (aOR 2.25, 95% CI 1.33-3.78; P=0.002) in those who had interpregnancy weight retention of 2 or more BMI units. However, this study used self-reported prepregnancy weight and no prior information on hypertension and GDM available (15). A large Swedish retrospective epidemiological study of 151,025 women who had their first two consecutive births between 1992 and 2001 found that those who gained 3 or more BMI units between pregnancies compared with those women whose BMI changed between -1.0 and 0.9 units had an adjusted odds ratio of GDM of 2.09 (1.68-2.61) (13). Wallace et al. (22) conducted a retrospective cohort study of 12,740 women in Aberdeen, Scotland who delivered their first and second children

between 1986 and 2007. Weight gain of greater than three BMI units was associated with an increase in large for gestational age infants. Jain et al. (23) analysed a population based historical cohort of 10,444 obese women in Missouri who delivered their first infant between 1998-2005. Interpregnancy weight gain was associated with an increased risk of a LGA infant (aOR 1.37; 95% CI, 1.21-1.54).

Our study is a prospective longitudinal illustrating that interpregnancy weight gain is associated with recurrent fetal macrosomia in a unique population of women who delivered a macrosomic baby ≥ 4.0 kg in their index pregnancy, and that interpregnancy weight gain of greater than the median is associated with an increased rate of GDM.

The interpregnancy interval is an important time for diet and lifestyle intervention in women who have delivered a macrosomic infant in their first pregnancy in the prevention of recurrent macrosomia and the development of GDM.

Strengths and Limitations

This longitudinal study has strengths. Maternal weight and height were measured at booking visit in each pregnancy <18 weeks gestation and BMI calculated accurately, rather than relying on maternal self-reporting. Furthermore, this cohort of women was uniform in that they delivered a first baby weight >4.0kg and they did not have GDM or hypertensive disorders in the first pregnancy. Data was prospectively collected by an investigator and accurately recorded into an anonymised computerised database.

A potential limitation of this study is that we do not have data on women who attended elsewhere for subsequent antenatal care. Another potential limitation is that the interpregnancy interval varied between subjects within this study. Finally, this study

applies to women who delivered a first baby >4kg, which applies to approximately 15% of our overall primiparous population.

Conclusions:

This longitudinal study demonstrates that within this cohort maternal interpregnancy weight change between a second and third pregnancy is associated with an increase in birthweight ≥ 4.0kg. Additionally a gain of more weight than the median (1.70kg) is associated with a higher rate of gestational diabetes. It is important to identify ways for women to maintain a normal weight and BMI throughout her life, particularly between pregnancies. Obstetricians should consider postnatal advice on interval pregnancy weight gain in order to reduce rates of macrosomia and gestational diabetes in future pregnancy in at risk women.

Acknowledgments

Nil of note

Contribution to Authorship

FMMcA conceived and designed the study. JW contributed to the study design and manuscript preparation. DAC performed the analysis and wrote the manuscript. RS performed analysis. All of the authors reviewed and revised the final version of the manuscript. FMMcA is the guarantor.

Ethical Approval

Not applicable

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Competing Interests

We have read and understood BMJ policy on declaration of interests and declare that we have no competing interests.

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Table 1: Demographics of the cohort at in the first trimester of the first, second and third pregnancies respectively (n=280)

	Pregnancy 1	Pregnancy 2	Pregnancy 3
Maternal Age (years)	29.0 (23.9,32.0)	31.8 (29.0,34.5)	34.8 (31.6,37.4)
Maternal Weight (kg)	68.8 (62.0,78.5)	71.4 (63.6,81.1)	73.1 (65.1,84.5)
BMI (kg/m^2)	24.9 (22.7,27.3)	25.7 (23.4,28.8)	26.0 (23.6,29.3)
Birthweight (kg)	4.2 (4.07,4.33)	4.1 (3.74,4.35)	4.0 (3.68,4.36)
Gestational Age (Days)	288 (282,292)	283 (277,288)	280 (273,287)
Obese ($\geq 30kg/m^2$)	11.4% (n=32)	20.0% (n=56)	22.1% (n=62)

All values are median with interquartile ranges (25^{th} and 75^{th}) in hypotheses, except for obesity (demonstrated in absolute numbers and percentages). Maternal weight and body mass index (BMI) were calculated at ≤ 18 weeks gestation.

Table 2:

Pregnancy outcomes for the third pregnancy based on those who gained inter-pregnancy weight compared with those who did not and those who gained more inter-pregnancy weight than the median compared with those who did not.

	Gained interpregnancy weight n=189	**Did not gain interpregnancy weight n=91**	**P value**
CS overall	41 (21.7%)	21 (23.1%)	NS
GDM	9 (4.8%)	2 (2.2%)	NS
BW ≥4kg	102 (54.0%)	36 (39.6%)	P=0.03
Hypertensive Disease	5 (2.6%)	2 (2.2%)	NS
NICU	4 (2.1%)	2 (2.2%)	NS
Stillbirth	1 (0.5%)	1 (1.1%)	NS
	Gained > 1.70kg inter-pregnancy weight (n=139)	**Gained ≤ 1.70kg inter-pregnancy weight (n=141)**	**P value**
CS overall	28 (20.1%)	34 (24.1%)	NS
GDM	9 (6.5%)	2 (1.4%)	0.03
BW ≥4kg	75 (54.0%)	63 (44.7%)	NS
Hypertensive Disease	4 (2.9%)	3 (2.1%)	NS
NICU	4 (2.9%)	2 (1.4%)	NS
Stillbirth	0 (0%)	2 (1.4%)	NS

Table 3. Effect of weight gain on odds of birthweight ≥4kg unadjusted and adjusted for maternal age and BMI calculated at less than 18 weeks gestation in the index pregnancy

	Unadjusted			Adjusted for maternal age and BMI		
	OR	95% CI	p-value	OR	95% CI	p-value
Weight gain from pregnancy 1 to 2	1.03	0.99, 1.07	0.169	1.05	1.01, 1.10	0.024
Weight gain from pregnancy 2 to 3	1.02	0.98, 1.06	0.243	1.03	0.99, 1.08	0.107
Weight gain from pregnancy 1 to 3	1.03	1.00, 1.06	0.093	1.04	1.01, 1.08	0.013

STROBE 2007 (v4) Statement—Checklist of items that should be included in reports of *cross-sectional studies*

Section/Topic	Item #	Recommendation	Reported on page #
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	2
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	3
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	5
Objectives	3	State specific objectives, including any prespecified hypotheses	6
Methods			
Study design	4	Present key elements of study design early in the paper	6
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	7
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants	6
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	7
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	7
Bias	9	Describe any efforts to address potential sources of bias	*N/A*
Study size	10	Explain how the study size was arrived at	
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	7
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	7
		(*b*) Describe any methods used to examine subgroups and interactions	N/A
		(*c*) Explain how missing data were addressed	N/A
		(*d*) If applicable, describe analytical methods taking account of sampling strategy	N/A
		(*e*) Describe any sensitivity analyses	N/A
Results			

Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	7
		(b) Give reasons for non-participation at each stage	N/A
		(c) Consider use of a flow diagram	N/A
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	7
		(b) Indicate number of participants with missing data for each variable of interest	N/A
Outcome data	15*	Report numbers of outcome events or summary measures	8
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	
		(*b*) Report category boundaries when continuous variables were categorized	8-9
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	N/A
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	N/A
Discussion			
Key results	18	Summarise key results with reference to study objectives	9
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	10-11
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	12
Generalisability	21	Discuss the generalisability (external validity) of the study results	12
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	N/A

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.