Reproductive Toxicology 71 (2017) 118–123

Contents lists available at ScienceDirect

Reproductive Toxicology

journal homepage: www.elsevier.com/locate/reprotox

Full length article

Does prednisone use or disease activity in pregnant women with rheumatoid arthritis influence the body composition of their offspring?

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ARTICLE INFO

Article history:
Received 29 July 2016
Received in revised form 25 April 2017
Accepted 2 May 2017
Available online 10 May 2017

Keywords:
Pregnancy
Rheumatoid Arthritis
RA disease activity
Prednisone use during pregnancy
Metabolic syndrome (in offspring)
Body composition (in offspring)

ABSTRACT

Glucocorticoids are given during pregnancy when rheumatoid arthritis (RA) is too active. It could lead to increased risk of cardiovascular diseases (CVD) and type 2 diabetes mellitus (T2DM) in the offspring. Elevated RA disease activity during pregnancy is associated with low birth weight and rapid post-natal growth. Both can negatively influence the body composition later in life. This study shows that prednisone use or RA disease activity in pregnant women with RA had no influence on the body composition of prepubertal offspring. Furthermore, no components of the metabolic syndrome (MetS) were present in the children, which minimalize the change on CVD or T2DM later in life. This reassuring conclusion might lead to a different therapeutic view when glucocorticoid treatment during pregnancy is inevitable.

1. Introduction

Choosing glucocorticoids as a medical treatment during pregnancy is always controversial, but sometimes inevitable. Glucocorticoids are given when pregnant women suffer from autoimmune diseases like rheumatoid arthritis (RA) or Crohn's disease. We hypothesize based on the following arguments that children who are born from mothers with active RA and/or children who have been exposed in utero to glucocorticoids could have an unfavorable health profile later in life.

First, our previous study found an association between maternal prednisone use and preterm delivery [1]. Preterm delivery has been associated with an unfavorable health profile later in life [2]. Second, several studies have shown that women with RA are at increased risk for giving birth to small for gestational age (SGA) infants [3]. In addition, it has been shown that active RA is associated with lower birth weight (although still within the normal range) and rapid catch up growth [1,4]. Not only SGA and rapid catch up growth can increase the risk to develop cardiovascular diseases (CVD) or type 2 diabetes mellitus (T2DM) later in life [5,6], but also lower birth weight, that still is in the normal range, has been associated with an increased risk of cardiovascular and metabolic disease in adulthood [7] Third, daytime cortisol level is elevated in prepubertal children when they were exposed to glucocorticoids in utero [8]. High cortisol levels in childhood have a negative influence on the health profile in adulthood [9]. Fourth, animal studies have suggested that in utero exposure to glucocorticoids can lead to increased glucocorticoid effect, creating a higher risk to develop CVD or T2DM [10]. In humans it is suggested that in utero exposure to glucocorticoids is limited since it is rapidly inactivated in the placenta. However, the placenta is only present after 10 weeks of gestation. Glucocorticoids can passively diffuse to the fetus at an early stage. Furthermore, pro-inflammatory cytokines, which are associated with active RA, can decrease this inactivation in the placenta [11,12].

To assess this risk on unfavorable health profiles at an early stage we evaluated the body composition and the presence of metabolic syndrome (MetS) during childhood. Body composition includes the total amount of lean body mass (LBM) and fat mass (FM). It is known that a higher fat percentage results in an increased risk for CVD and T2DM [13]. MetS is a combination of 5 related cardiovascular risk factors: abdominal obesity, high triglyceride (TG), low high-

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http://dx.doi.org/10.1016/j.reprotox.2017.05.002

density lipoproteïne (HDL), high systolic or diastolic pressure and high fasting glucose. MetS is defined as the presence of 3, or more of these risk factors [14].

The main aim of this study was to investigate the association of maternal prednisone use and elevated RA disease activity during pregnancy with the body composition of the prepubertal child. The second aim was to assess the prevalence of early CVD or T2DM determinants by MetS components. We therefore studied the prepubertal offspring of mothers with RA and identified the early determinants by fat distribution, lipid levels and blood pressure. All of these mothers participated in a prospective study on RA and pregnancy, therefore detailed information on medication and disease activity was present. Previously, we have shown in this cohort that active RA during pregnancy was associated with lower birth weight SDS and that the use of prednisone during pregnancy was associated with shorter gestational age [1] .We now extend our observations to the same group of children but now at a mean age of seven. If prednisone or RA disease activity would affect these determinants, the offspring might have a higher risk for a less favorable future health profile.

2. Materials & methods

The study cohort consisted of 108 healthy children born to mothers participating in the PARA-study (Pregnancy-induced Amelioration of Rheumatoid Arthritis). The PARA-study was described in detail previously [15]. In summary, women were eligible for the study if they met the 1987 ACR criteria for RA, had a pregnancy wish or were already pregnant, and had a good understanding of the Dutch language. In this prospective, nationwide cohort study, women with RA were visited during every trimester at their home address by a member of the research team who performed a physical examination and collected information on disease activity including medication use [15]. RA disease activity (DAS28CRP) was calculated by examining 28 joints and using 2 variables for each joint: number of swollen joints, number of tender joints, and measuring serum C-reactive protein (CRP) level [16,17].

Of the 108 children born 3 were a twin pregnancy leading to 105 mothers participating in this study. All children were born between 2002 and 2006. Medication during pregnancy was used by 59% (62/105) of the mothers and restricted to prednisone (26%), a combination of prednisone and sulfasalazine (15%), sulfasalazine (16%), hydroxychloroquine (1%) or a combination of sulfasalazine and hydroxychloroquine (1%) (Table 1). The median dose of prednisone was 6.2 mg/day with a interquartile range of 1–15 mg/day. The median sulfasalazine dose was 2000 mg/day with a interquartile range 500–4000 mg/day.

Medical records were used to confirm gestational age. The mean gestational age was 39.4 weeks and less than 5% (n = 5) of the mothers smoked during pregnancy. Birth weight was expressed as birth weight standard deviation scores (birth weight SDS), corrected for gestational age and gender [18]. The mean birth weight SDS was 0.03 (SD: 1.13). All mothers who participated in the PARA-study were contacted by mail. Growth charts of the children were collected in the first few years of life and when the child was over the age of 5 years they were invited to visit the Sophia Children's Hospital. This age was chosen due to ethical reasons and because normal values on DXA-scan before this age are lacking. Differences between study population and those who were unwilling to participate or lost-to-follow up were investigated with *t*-tests for continuous variables and with χ^2 tests for measured categorical variables.

Anthropometric measurements consisted of height, weight, sitting height and head, arm and waist circumference. All measurements were executed by the same doctor and with the same scale.

Table 1
Characteristics of Mother and Child.

Clinical Characteristics Mother (n = 105)	mean (SD)	
age at delivery (years)	32.5 (3.81)	
RA duration at delivery (years)	7.49 (6.33)	
RA disease activity *		
first trimester	3.65 (1.19)3.33 (1.18)	
third trimester		
Use of Medication during pregnancy	n (%)	
no medication	43 (41)	
only prednisone	27 (26)	
only sulfasalazine	17 (16)	
only hydroxychloroquine	1 (1)	
prednisone + sulfasalazine	16 (15)	
sulfasalazine + hydroxychloroquine	1 (1)	
Clinical Characteristics Child (n = 108)	mean (SD)	
At Birth		
gender (M/F)	60/48	
birth weight in kilograms	3.37 (0.8)	
gestational age in weeks	39.4 (1.8)	
birth weight SDS	0.03 (1.13)	
At 7-years-old		
age (years)	6.90 (1.24)	
weight SDS	0.07 (1.70)	
height SDS	0.05 (0.98)	
DXA		
LBM SDS	−0.65 (0.70)	
FM SDS	0.21 (0.94)	
%TF	0.35 (0.04)	
BMI SDS	−0.18 (0.88)	
Circumferences		
arm SDS	−0.02 (1.61)	
waist SDS	0.18 (1.06)	
hip SDS	−0.55 (1.06)	
waist:hip SDS	1.03 (0.92)	
MetS components		% abnormal
waist circumference (cm)	55.96 (6.28)	9
fasting Triglycerides (mmol/L)	0.81 (0.29)	17
fasting HDL (mmol/L)	1.50 (0.29)	2
systolic BP (mm HG)	96.9 (9.5)	2
diastolic BP (mm HG)	56.5 (6.6)	0
fasting Glucose (mmol/L)	4.91 (0.40)	3

All data are expressed as mean (SD) or number (%).
*RA disease activity is calculated using the DAS28CRP score. Abbreviations: RA, rheumatoid arthritis; SDS, Standard Deviation Score; DXA, Dual-energy X-ray absorptiometry; LBM, lean body mass; FM, fat mass; %TF, trunk fat percentage; BMI, body mass index; MetS, metabolic syndrome; BP, blood pressure; HDL, High-Density Lipoprotein.

Measurements were performed 3 times and the mean value was used for analysis.

To measure lean body mass (LBM) and fat mass (FM), a DXA-scan was performed (Dual-Energy X-ray Absorptiometry scan, type Lunar-Prodigy; GE Healthcare, Chalfont St. Giles, UK). All scans were made on the same machine and quality assurance was performed daily. Coefficient of variation was 0.7% for LBM and 1.2% for FM [19–21]. Trunk fat percentage (TF%) was calculated as fat mass $_{trunk}$/fat mass $_{totalbody}$. Body mass index (BMI) was calculated by dividing weight (kilograms) by the square of height (meters). LBM, FM and BMI values were transformed into SDS for age and gender according to Dutch reference data for children [22].

The following definitions were used for the MetS components: abdominal obesity (waist circumference ≥ 90th percentile), TG levels ≥ 95th percentile of the general population with similar age (TG ≥ 1.1 mmol/L), HDL ≤ 95th percentile of the general population with similar age (HDL ≤ 0.9 mmol/L), high blood pressure (systolic or diastolic ≥ 90th percentile) and fasting glucose ≥ 95th percentile of the general population with similar age (glucose ≥5.6 mmol/L)[14]. Since no definition for the metabolic syndrome has been defined and validated in children <10 years of age, it was

primarily chosen to study the individual MetS components separately, and use as cut off levels those precentiles that are also commonly used in older age groups as well as adults.

Fasting blood samples were collected between 0800 and 1000 h, to determine glucose, and lipid profile. One child was excluded from analyses concerning MetS due to a non-fasting blood sample. Plasma glucose, total cholesterol, high-density lipoprotein (HDL) and triglycerides (TG) were measured on a Roche modular P analyser (Roche Diagnostics, Almere, The Netherlands). After centrifugation, samples were frozen at −80 °C until analysed. Our study was approved by the Medical Ethics Committee, Erasmus MC (Rotterdam, The Netherlands). All parents gave their written informed consent.

A power calculation was made before starting the study. It was based upon the research question whether the main outcome measures, like LBM SDS or FM SDS of children at age of 7 years old, is related to maternal disease activity during pregnancy, as expressed in DAS28CRP. DAS28CRP has a normal distribution and a known SD of 1.2 and by definition a SDS has a mean of 0.0 and a SD of 1.0 [23]. Therefore, one can calculate that n = 83 children are needed if the true correlation between DAS28CRP and LBM or FM SDS has a slope of 0.25 (indicating that a difference in DAS28CRP of 2.0 results in a mean difference of 0.5 SDS for LBM or FM) with a power of 80% and a $p < 0.05$. A difference of SDS 0.5 was chosen, because this is considered to be the smallest meaningful difference.

2.1. Statistical analysis: body composition

To compare the body composition with age and sex matched references a one-sample *t*-test was used comparing the LBM SDS and FM SDS results with zero.

Multiple linear regression (MR) analyses were performed to determine the association between the child-related variables; age, gender, birth weight SDS, height SDS and weight SDS with the body composition outcomes, LBM SDS and FM SDS. These child-related variables are known to be associated with the body composition of the child and were analysed to examine the potential added value of RA-related variables namely, prednisone use, sulfasalazine use, and RA disease activity during pregnancy.

Per body composition outcome, 5 models were designed to determine the added value of the RA-related variables. We first entered only prednisone in the model (Model A), then only sulfasalazine (Model B) followed by the use of both prednisone and sulfasalazine (Model C). Fourth, RA disease activity was put in separately (Model D) and finally all variables were added to investigate the association between all RA-related variables combined and LBM or FM (Model E). All models were adjusted for the child-related variables studied (age, gender, birth weight SDS, height SDS and weight SDS). Interaction terms were investigated for all RA variables. When significant, the term was entered in the model when both variables were present. This lead to the following interaction terms; prednisone*weight SDS ($p < 0.001$), sulfasalazine*height SDS ($p < 0.05$) and RA disease activity*birth weight SDS ($p < 0.05$).

2.2. Statistical analysis: metabolic syndrome

Concerning the presence of metabolic syndrome (MetS), we first evaluated the prevalence of each of the 5 MetS components. Differences in prevalence of each MetS component was investigated with *t*-tests for the continuous, independent variable, RA disease activity and with $\chi 2$ tests for the categorical, independent variables, prednisone and sulfasalazine. If a significant difference in prevalence was found, a multiple linear regression model was designed to determine the association of the RA-related variables prednisone, sulfasalazine and RA disease activity and the MetS component as a continuous variable. This multiple linear regression model was designed similarly to the model described above for analysing the body composition. All statistical analyses were performed using STATA software (version 12.0 for Mac; StataCorp LP, Texas, USA). Statistical significance was defined as $p < 0.05$.

Table 2
Multiple linear regression-analyse.

Associations of child-related variables				
	LBM SDS		FM SDS	
Variables	β	p-value	β	p-value
Age (years)	−0.02	0.40	0.14	0.02
Gender (m/f)	−0.27	<0.001	0.01	0.98
Birth weight (SDS)	0.15	<0.001	−0.06	0.41
Height (SDS)	0.47	<0.001	0.34	<0.001
Weight (SDS)	0.05	0.03	0.20	<0.001
Overall	<0.001		<0.001	
R^2-adjusted	0.75		0.37	

Abbreviations: LBM, Lean Body Mass; FM, Fat Mass; SDS, standard deviation score

3. Results

A total of 55% (108/196) of all eligible children participated in the study. No differences in characteristics were found between the study population (n = 108) and those who were unwilling to participate (n = 75) or lost-to-follow-up (n = 13). The main reasons for non-participation was the traveling to the hospital (38%) and the fact that parents felt that our investigations were too much of a burden for their child (30%).

The mean age (SD) of our study population was 6.90 (1.24) years. The mean (SD) weight SDS was 0.07 (1.70) and height SDS 0.05 (0.98), all within normal range (Table 1). Both weight and height were associated with the RA disease activity during pregnancy, β = −0.31, p = 0.03 and β = −0.21, p = 0.01, respectively. After adjustment for birth weight SDS, these associations disappeared.

3.1. Body composition

The mean (SD) LBM SDS was −0.65 (0.70) and FM SDS was 0.21 (0.94). Both LBM SDS ($p < 0.001$) and FM SDS ($p = 0.02$) were different from the reference mean. Although these results are within normal ranges it does show a lower LBM and a higher FM, indicating that our population had moderately more FM than LBM (Table 1).

The child-related variables, age, gender, birth weight SDS, height SDS and weight SDS were all highly associated with LBM SDS and FM SDS. In the MR-analysis concerning LBM SDS, the explained variance (adjusted R^2) was 0.75 and gender, birth weight SDS and height SDS were all strongly significant determinants ($p < 0.001$). In the FM SDS analysis (adjusted $R^2 = 0.37$) current height and weight of the child were most important ($p < 0.001$) (Table 2). To examine the potential added value of RA-related variables during pregnancy, the RA-related variables were added separately resulting in 5 models per body composition outcome.

3.2. Lean body mass

Model A shows that prednisone use during pregnancy was not significantly associated with LBM SD. Sulfasalazine was also not associated with LBM when analysed separately (Model B) or in combination with prednisone (Model C). RA disease was no significant determinant of LBM (Model D). The final model illustrates that the combination of all RA-related variables during pregnancy were not associated with LBM and the adjusted R^2 hardly increased from 0.75 (Table 2) to 0.78 (Table 3).

Table 3
Multiple linear regression-analyse – Associations of RA-related variables and LBM SD or FM SD*.

	Model A		Model B		Model C		Model D		Model E	
LBM SD	β	p	β	p	β	p	β	p	β	p
Prednisone	0.02	0.81			0.001	0.99			−0.04	0.63
Sulfasalazine			0.08	0.27	0.08	0.25			0.11	0.13
RA disease activity							0.02	0.61	0.01	0.76
Overall	<0.001		<0.001		<0.001		<0.001		<0.001	
R^2-adjusted	0.76		0.76		0.77		0.75		0.78	
FM SD	β	p	β	p	β	p	β	p	β	p
Prednisone	−0.21	0.14			0.02	0.81			0.02	0.81
Sulfasalazine			−0.21	0.17	−0.18	0.22			−0.22	0.14
RA disease activity							−0.07	0.30	−0.08	0.20
Overall	<0.001		<0.001		<0.001		<0.001		<0.001	
R^2-adjusted	0.47		0.39		0.49		0.38		0.48	

* All models are adjusted for child-related variables; age, gender, birth weight SDS, height SDS, weight SDS (see Table 2) and an interaction term when both variables are present; RA disease activity is calculated using the DAS28CRP score.

3.3. Fat mass

In Model A, prednisone was not significantly associated with FM SD. When sulfasalazine was inserted separately (Model B) or in combination with prednisone (Model C), no association with FM SD was present. Also RA disease activity showed no significant association with FM SD (Model D). The final model illustrates that prednisone, sulfasalazine or RA disease activity during pregnancy are not associated with FM. In this Model E, the explained variance increased from 0.38 to 0.48 (Table 3)

3.4. Metabolic syndrome (MetS)

Abdominal obesity represented by waist circumference was present in 9% (10/108) of the children. Furthermore, high TG was present in 17% (17/103) of the children, low HDL in 2% (2/103), high blood pressure in 2% (2/106) and high fasting glucose in 3% (3/102). RA disease activity during pregnancy was significantly lower in the offspring with higher waist circumference ($p = 0.02$) and was therefore further analysed in a MR analysis. There were no other associations found between RA related variables during pregnancy and the prevalence within each MetS component (Table 4). Only one child had three or more components of the MetS. The prevalence of MetS in our population was therefore 1%. Due to this low percentage, no statistical analyses were performed.

3.5. Waist circumference

MR analysis was performed using waist circumference as continues variable (Table 5). No significant association was seen with prednisone (Model A), or sulfasalazine (Model B). Model C demonstrates that when prednisone and sulfasalazine are assessed together there is no influence on the waist circumference. RA disease activity was not significantly associated with waist circumference (Model D). The apparent association seen in Table 4 between RA disease activity and waist circumference had completely disappeared after adjustment (Table 5).

4. Discussion

Prednisone use and/or elevated RA disease activity during pregnancy in women with RA had no influence on the body composition in offspring of approximately 7-years-old. Furthermore, no association was found between medication and/or elevated RA disease activity and early determinants for CVD and T2DM. However, one should keep in mind that medication use and elevated RA disease activity are not independent variables, since medication is prescribed in patients with active disease in order to lower disease activity.

Seventeen percent of the children in this study showed an increased level of triglyceride, since a comparison group is lacking, the interpretation of these data is difficult. We also found several child-related variables significantly influencing the lean body mass and the fat mass, like age, gender, birth weight, height and weight. These associations were comparable with the normal population suggesting a normal development of the child.

A significant association between elevated RA disease activity and lower birth weight has been shown [1]. Lower birth weight, even within the normal range, has been associated with lower lean body mass and higher fat mass [7]. One would expect that low birth weight due to the high RA disease activity, generates an effect-modifying outcome of RA disease activity on body composition, yet no such association was found. Nevertheless, based on our previous study, we emphasize that elevated RA disease activity should be avoided during pregnancy, highlighting the important role for medication [3,15,24]. We found that active RA during pregnancy was associated with lower weight and height of the children at age seven. These associations, however, disappeared after correction for birth weight SDS, suggesting that there was no direct effect of disease activity.

Importantly, this study shows that maternal glucocorticoid use during pregnancy does not influence the body composition of the offspring or the presence of determinants of adult diseases. Glucocorticoids can be given when an autoimmune disease, like RA or Crohn's disease complicates a pregnancy. Experimental studies in animals showed an increased risk of the development of adult disease following maternal glucocorticoid treatment during pregnancy, suggesting a re-setting of the hypothalamic-pituitary-adrenal axis due to low birth weight and glucocorticoid overexposure [10]. No studies have actually found a direct association between maternal glucocorticoid treatment during pregnancy and adult diseases like CVD and T2DM, but an indirect association on the presence of more risk factors have been described [10]. Our study shows that these risk factors are not present at approximately 7-years of age.

The metabolic syndrome includes a cluster of cardiovascular risk factors that have been shown to predict the development of CVD and T2DM. The main hypothesis explaining this syndrome is the dysfunction of adipocytes in genetically prone persons, which lead to insulin resistance and subclinical inflammation, creating atherosclerosis and apparent clinical manifestations [25]. In 2007, the International Diabetes Federation attempted to define the metabolic syndrome in children. Discussion is still ongoing if it is feasible to create such a definition for children, partly due to the

Table 4
Prevalence of each MetS component and RA-related variables during pregnancy.

	MetS component present	RA disease activity (*t*-test)		Prednisone use (Pearson chi^2)		Sulfasalazine use (Pearson chi^2)	
MetS components	%	diff.	p-value	N/Y	p-value	N/Y	p-value
Waist circumference	9 (10/108)	0.90	**0.02**	7/3	0.43	5/5	0.21
Triglycerides	17 (17/103)	0.20	0.52	8/9	0.26	11/6	0.30
HDL	2 (2/103)	1.00	0.23	2/0	0.24	2/0	0.32
BP	2 (2/106)	−0.71	0.41	1/1	0.78	1/1	0.61
Glucose	3 (3/102)	−0.01	0.99	3/0	0.15	1/2	0.21
MetS	1(1/102)	na	na	na	na	na	na

Abbreviations: RA, Rheumatoid Arthritis; HDL, High-density lipoprotein; BP, Bloodpressure; MetS, metabolic syndrome (≥3 components present); diff, differences in mean disease activity between the Mets present and the Mets absent groups; N/Y, No/Yes; na, not applicable due to the small number; RA disease activity is calculated using the DAS28CRP score.

Table 5
MR-analyse – Associations between waist circumferences in cm and RA-related variables*.

	Model A		Model B		Model C		Model D		Model E	
Waist circumferences	β	p	β	p	β	p	β	p	β	p
Prednisone use	−1.09	0.15			−0.50	0.54			−0.65	0.43
Sulfasalazine use			−0.50	0.54	−0.32	0.68			−0.24	0.77
RA activity							−0.37	0.30	−0.43	0.22
Overall	<0.001		<0.001		<0.001		<0.001		<0.001	
R^2-adjusted	0.71		0.68		0.72		0.66		0.71	

* All models are adjusted for child-related variables; age, gender, birth weight SDS, height SDS, weight SDS (see Table 2) and an interaction term when both variables are present; RA disease activity is calculated using the DAS28CRP score.

great variance within the pediatric population. Furthermore, the actual outcome (developing CVD or T2DM) is probably still decades away. One of the solutions is to focus on the prevalence of each of the MetS components and not on the whole syndrome. The prevalence of the components in our group was extremely low (0–3%) and all were comparable to the normal population. Kerkhof et al. demonstrated that higher gain in weight for lengths in the first 3 months of life (rapid catch up growth) is associated with a higher prevalence of several MetS components at the age of 21 years [26]. Our previous study showed that elevated RA disease activity during pregnancy was positively associated with rapid catch up growth, which is associated with the prevalence of MetS [15,26]. In present study we found no association between prednisone use or RA disease activity and the prevalence of the MetS components. When investigating the effect of prednisone or RA disease activity during pregnancy all co-medication was taken into account. Almost half of all the women used prednisone during pregnancy in combination with sulfasalazine. In the multiple linear regression-analyses no association was found between sulfasalazine and any of the MetS components.

A total of 55% of all eligible children participated in the study. Although there was no statistical difference between the participating and non-participating group, there could be a bias. In addition, although being a large study in it's kind, only 43 pregnancies exposed to prednisone were studied. Furthermore, we want to emphasize that although we did not find any association at prepubertal age, only long-term follow-up, preferably at young adult age, has to be performed to determine whether these children will maintain normal body compositions and will not develop any signs of MetS.

5. Conclusion

Our study shows that prednisone use and/or elevated RA disease activity during pregnancy has no influence on the body composition of the approximately 7-years old offspring. Furthermore, no clinical purpose like early determinants for CVD and T2DM were present at this age. This reassuring conclusion might lead to a different therapeutic view on glucocorticoid treatment in pregnant women, but cannot be extrapolated beyond the age of 7 years. Only follow-up studies of these children will give a definite answer. Such studies should include puberty when marked changes in body composition occur.

Acknowledgements

We would like to thank all parents and their children for their voluntary contributions. We would like to emphasize the great effort made by dr Y.A. de Man and dr F.E. van de Geijn in obtaining most the PARA data. We are grateful to the research assistants, for data collection, and all laboratory technicians, for their assistance with laboratory research. This study was supported by the Dutch Arthritis Association; a non-profit fund-raising organization (DAA 08-1-306). 1:26-32.

References

[1] Y.A. de Man, J.M. Hazes, H. van der Heide, S.P. Willemsen, C.J. de Groot, E.A. Steegers, et al., Association of higher rheumatoid arthritis disease activity during pregnancy with lower birth weight: results of a national prospective study, Arthritis Rheum. 60 (2009) 3196–3206.
[2] G.F. Kerkhof, P.E. Breukhoven, R.W. Leunissen, R.H. Willemsen, A.C. Hokken-Koelega, Does preterm birth influence cardiovascular risk in early adulthood? J. Pediatr. 161 (390-6) (2012) e1.
[3] H. Ince-Askan, R.J. Dolhain, rheumatoid arthritis, Best Pract. Res. Clin. Rheumatol. 29 (2015) 580–596.
[4] F.D. de Steenwinkel, A.C. Hokken-Koelega, M.A. de Ridder, J.M. Hazes, R.J. Dolhain, Rheumatoid arthritis during pregnancy and postnatal catch-up growth in the offspring, Arthritis Rheumatol. 66 (2014) 1705–1711.
[5] R.W. Leunissen, T. Stijnen, A.C. Hokken-Koelega, Influence of birth size on body composition in early adulthood: the programming factors for growth and metabolism (PROGRAM)-study, Clin. Endocrinol. (Oxf.) 70 (2009) 245–251.
[6] G.F. Kerkhof, R.H. Willemsen, R.W. Leunissen, P.E. Breukhoven, A.C. Hokken-Koelega, Health profile of young adults born preterm: negative effects of rapid weight gain in early life, J. Clin. Endocrinol. Metab. 97 (2012) 4498–4506.
[7] K.K. Ong, D.B. Dunger, Perinatal growth failure: the road to obesity, insulin resistance and cardiovascular disease in adults, Best Pract. Res. Clin. Rheumatol. 16 (2002) 191–207.
[8] F.D. de Steenwinkel, A.C. Hokken-Koelega, J.M. Hazes, R.J. Dolhain, The influence of foetal prednisone exposure on the cortisol levels in the offspring, Clin. Endocrinol. (Oxf.) 80 (2014) 804–810.

[9] T.G. O'Connor, Y. Ben-Shlomo, J. Heron, J. Golding, D. Adams, V. Glover, Prenatal anxiety predicts individual differences in cortisol in pre-adolescent children, Biol. Psychiatry 58 (2005) 211–217.
[10] E.C. Cottrell, J.R. Seckl, Prenatal stress, glucocorticoids and the programming of adult disease, Front. Behav. Neurosci. 3 (2009) 19.
[11] P. Charles, M.J. Elliott, D. Davis, A. Potter, J.R. Kalden, C. Antoni, et al., Regulation of cytokines, cytokine inhibitors, and acute-phase proteins following anti-TNF-alpha therapy in rheumatoid arthritis, J. Immunol. 163 (1999) 1521–1528.
[12] I. Kossintseva, S. Wong, E. Johnstone, L. Guilbert, D.M. Olson, B.F. Mitchell, Proinflammatory cytokines inhibit human placental 11beta-hydroxysteroid dehydrogenase type 2 activity through Ca2+ and cAMP pathways, Am. J. Physiol. Endocrinol. Metab. 290 (2006) E282–8.
[13] M. Cnop, J. Vidal, R.L. Hull, K.M. Utzschneider, D.B. Carr, T. Schraw, et al., Progressive loss of beta-cell function leads to worsening glucose tolerance in first-degree relatives of subjects with type 2 diabetes, Diabetes Care 30 (2007) 677–682.
[14] S.M. Grundy, J.I. Cleeman, C.N. Merz, H.B. Brewer Jr., L.T. Clark, D.B. Hunninghake, et al., Implications of recent clinical trials for the national cholesterol education program adult treatment panel III guidelines, Circulation 110 (2004) 227–239.
[15] Y.A. de Man, R.J. Dolhain, F.E. van de Geijn, S.P. Willemsen, J.M. Hazes, Disease activity of rheumatoid arthritis during pregnancy: results from a nationwide prospective study, Arthritis Rheum. 59 (2008) 1241–1248.
[16] Y.A. de Man, J.M. Hazes, F.E. van de Geijn, C. Krommenhoek, R.J. Dolhain, Measuring disease activity and functionality during pregnancy in patients with rheumatoid arthritis, Arthritis Rheum. 57 (2007) 716–722.
[17] P. Van Riel, A. van Gestel, D. Scott, Interpreting disease course, in: P. van Riel, A. Van Gestel, D. Scott (Eds.), Eular Handbook of Clinical Assessments in Rheumatoid Arthritis, Alphen aan den Rijn: Van Zuiden Communications B.V, 2000, pp. 39–43.
[18] A. Niklasson, A. Ericson, J.G. Fryer, J. Karlberg, C. Lawrence, P. Karlberg, An update of the Swedish reference standards for weight, length and head circumference at birth for given gestational age (1977–1981), Acta Paediatr. Scand. 80 (1991) 756–762.
[19] S.L. Bonnick, C.C. Johnston Jr., M. Kleerekoper, R. Lindsay, P. Miller, L. Sherwood, et al., Importance of precision in bone density measurements, J. Clin. Densitom. 4 (2001) 105–110.
[20] G.M. Kiebzak, L.J. Leamy, L.M. Pierson, R.H. Nord, Z.Y. Zhang, Measurement precision of body composition variables using the lunar DPX-L densitometer, J. Clin. Densitom. 3 (2000) 35–41.
[21] J.A. Shepherd, B. Fan, Y. Lu, E.M. Lewiecki, P. Miller, H.K. Genant, Comparison of BMD precision for Prodigy and Delphi spine and femur scans, Osteoporos. Int. 17 (2006) 1303–1308.
[22] A.M. Boot, J. Bouquet, M.A. de Ridder, E.P. Krenning, S.M. de Muinck Keizer-Schrama, Determinants of body composition measured by dual-energy X-ray absorptiometry in Dutch children and adolescents, Am. J. Clin. Nutr. 66 (1997) 232–238.
[23] P.L. van Riel, L. Renskers, The Disease Activity Score (DAS) and the Disease Activity Score using 28 joint counts (DAS28) in the management of rheumatoid arthritis, Clin. Exp. Rheumatol. 34 (Suppl. 101) (2016) 40–44.
[24] F.D. de Steenwinkel, A.C. Hokken-Koelega, Y.A. de Man, Y.B. de Rijke, M.A. de Ridder, J.M. Hazes, et al., Circulating maternal cytokines influence fetal growth in pregnant women with rheumatoid arthritis, Ann. Rheum. Dis. 72 (12) (2013 Dec) 1995–2001, http://dx.doi.org/10.1136/annrheumdis-2012-202539, Epub 2012 Dec 21.
[25] A. Guilherme, J.V. Virbasius, V. Puri, M.P. Czech, Adipocyte dysfunctions linking obesity to insulin resistance and type 2 diabetes, Nat. Rev. Mol. Cell Biol. 9 (2008) 367–377.
[26] G.F. Kerkhof, R.W. Leunissen, A.C. Hokken-Koelega, Early origins of the metabolic syndrome: role of small size at birth, early postnatal weight gain, and adult IGF-I, J. Clin. Endocrinol. Metab. 97 (2012) 2637–2643.