A retrospective study of the pregnancy, delivery and neonatal outcome in overweight versus normal weight women with polycystic ovary syndrome

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Submitted on January 17, 2014; resubmitted on May 11, 2014; accepted on May 21, 2014

STUDY QUESTION: Do overweight women with polycystic ovary syndrome (PCOS) have a higher risk of perinatal complications than normal weight women with PCOS?

SUMMARY ANSWER: Overweight women with PCOS with an ongoing singleton pregnancy have an increased risk of preterm birth as well as an increased risk of giving birth to a baby with a higher birthweight than normal weight women with PCOS.

WHAT IS KNOWN ALREADY: There is evidence that overweight (BMI ≥ 25 kg/m²) has a negative influence on the prevalence of gestational diabetes mellitus and fetal macrosomia in women with PCOS.

STUDY DESIGN, SIZE, DURATION: We set up a retrospective comparative cohort study of 93 overweight (BMI ≥ 25 kg/m²) and 107 normal weight (BMI < 25 kg/m²) women with PCOS who were scheduled for fertility treatment between January 2000 and December 2009 and achieved a pregnancy as a result of a treatment cycle, or spontaneously before or between treatment cycles.

PARTICIPANTS/MATERIALS, SETTING, METHODS: All data (patient characteristics, medical information, pregnancy, delivery and neonatal outcome) were retrieved from patient medical files. All pregnancy, delivery and neonatal outcome parameters were adjusted for age and pre-pregnancy smoking behaviour. The neonatal outcome parameters were additionally adjusted for gestational age.

MAIN RESULTS AND THE ROLE OF CHANCE: The median BMI in the overweight and normal weight women was, respectively, 30.8 kg/m² [interquartile quartile range (IQR) 5.8] and 20.9 kg/m² (IQR 2.3) (P < 0.001). Baseline characteristics did not differ between groups, except for free testosterone and fasting insulin levels, which were higher, and sex hormone-binding globulin, which was lower, in overweight versus normal weight women (all P < 0.001). The time-to-pregnancy was significantly higher in the overweight group (P = 0.01). Multivariate analyses of the ongoing singleton pregnancies showed significantly more preterm births in overweight (10/61) versus normal weight (2/71) women [adjusted odds ratio 0.1, 95% confidence interval (CI) 0–0.6, P = 0.01]. The mean birthweight of newborns was significantly higher in overweight (3386 ± 663 g) than in normal weight (3251 ± 528 g) women (adjusted mean difference 259.4, 95% CI 83.4–435.4, P = 0.004).

LIMITATIONS, REASON FOR CAUTION: Our results only represent the pregnancy, delivery and neonatal outcome of ongoing singleton pregnancies. The rather small sample size and observational nature of the study are further limitations.

WIDER IMPLICATIONS OF THE FINDINGS: Our results suggest the importance of pre-pregnancy weight loss in overweight women with PCOS in order to reduce the risk of adverse perinatal outcomes.

STUDY FUNDING/COMPETING INTEREST(S): Veerle De Frènè is holder of a Special PhD Fellowship by the Flemish Foundation for Scientific Research (FWO-Vlaanderen). Petra De Sutter is holder of a fundamental clinical research mandate by the Flemish Foundation for Scientific Research (FWO-Vlaanderen). There are no competing interests.

Key words: polycystic ovary syndrome / overweight / pregnancy complications / delivery / newborn
Introduction

Polycystic ovary syndrome (PCOS) is an endocrine disorder present in ~5–10% of women of reproductive age (Hoeger et al., 2004; Broekmans et al., 2006). It is characterized by the presence of oligo- or amenorrhoea, polycystic ovaries, hirsutism, raised LH:FSH ratio, insulin resistance (IR) and compensatory hyperinsulinemia (The Rotterdam ESHRE/ASRM-sponsored consensus workshop group, 2004). IR has an important influence on the development of diabetes type 2 and hypertension (Perciaccante et al., 2006). Hypertension is thought to be associated with androgen excess and a subsequent increased stimulation of sympathetic nerve activity (Perciaccante et al., 2007; Studen et al., 2013). Abdominal overweight and obesity—also important components of PCOS that affect ~30–70% of the PCOS population (Pasquali et al., 2006; Vrbikova and Hainer, 2009)—are associated with IR, increased testosterone production (Pasquali et al., 2006) and increased stimulation of sympathetic nerve activity (Troisi et al., 1991; Scherrer et al., 1994).

Polycystic ovary syndrome in itself has a negative influence on the perinatal outcome for these women. There is evidence that women with PCOS are at increased risk of early pregnancy loss and miscarriages (Wang et al., 2001), which could possibly be caused by pre-pregnancy LH hypersecretion (Regan et al., 1990), hyperandrogenemia (Okon et al., 1998; Kazerooni et al., 2013), overweight (Fedorscak et al., 2000), hyperinsulinemia and/or thrombophilia (Kazerooni et al., 2013). In women with PCOS, pregnancy is often complicated by pregnancy-induced hypertension, pre-eclampsia and gestational diabetes mellitus (GDM) and also the risk for a preterm delivery or a delivery by Caesarean section is raised (Boomsma et al., 2006; Alberi et al., 2010; Kjeruff et al., 2011; Qin et al., 2013). The newborn babies stay more frequently in a neonatal intensive care unit and perinatal mortality also occurs more frequently (Boomsma et al., 2006; Qin et al., 2013). Since it has been proved that pre-pregnancy maternal overweight and obesity have a negative influence on the perinatal outcome (Bogaerts et al., 2012; Blomberg, 2013; Cnattingius et al., 2013; Crane et al., 2013), existing retrospective studies comparing the perinatal outcome in women with PCOS versus women without PCOS have matched the samples for BMI or have had the adjusted analyses for BMI. As such, Mikola et al. (2001) and Turhan et al. (2003), looking into the pregnancy, delivery and neonatal outcome in women with PCOS, concluded that pre-pregnancy overweight (BMI > 25 kg/m²) is an important predictor of GDM. A study by Han et al. (2011) of Asian women looked into the influence of overweight (BMI > 25 kg/m²) on the pregnancy outcome in women with PCOS, using a case–control design of overweight versus non-overweight women, and showed that the prevalence of GDM and fetal macrosomia was significantly higher in overweight versus normal weight women with PCOS.

Since these studies are rather scarce and, to date, only performed in an Asian population, we performed a retrospective cohort study comparing the pregnancy, delivery and neonatal outcome in overweight versus normal weight women with PCOS using multivariate analyses.

Materials and Methods

Design

A retrospective comparative cohort study was conducted at the Department of Reproductive Medicine of the Ghent University Hospital, Ghent, Belgium. The study population included 93 overweight and 107 normal weight women with PCOS between the ages of 18 and 43 years who were pregnant (i.e. positive hCG at 4 weeks after the start of the last menstrual cycle) as a result of a treatment cycle, or spontaneously before the start or between treatment cycles. All study participants were scheduled for a treatment at the fertility centre between January 2000 and December 2009. There was no upper BMI limit impeding women from undergoing a fertility treatment. Only the first pregnancy was taken into account. PCOS was diagnosed using the diagnostic criteria of the Rotterdam consensus 2003 (The Rotterdam ESHRE/ASRM-sponsored PCOS consensus workshop group, 2004). Women scheduled for a fertility treatment between 2000 and 2003 were reclassified as PCOS patients according to the Rotterdam criteria. Those women who fulfilled these criteria were included in the study. Women with pathologies (such as congenital adrenal hyperplasia, Cushing’s syndrome and androgen-secreting tumors) which present or imitate the same characteristics as PCOS were excluded. All data (patient characteristics, medical information, pregnancy, delivery and neonatal outcome) were retrieved from patient medical files. If delivery took place in another hospital, data on pregnancy, delivery and neonatal outcome were obtained through the treating gynaecologist of that hospital.

Measures

A polycystic ovarian morphology (PCOM) was diagnosed by means of transvaginal ultrasound showing the presence of ≥ 12 follicles with a diameter of 2–9 mm and/or an increased ovarian volume of > 10 cm³ (using the formula 4/3π abc). Participants were described as having an irregular menstrual cycle if they had oligomenorrhoea (i.e. no menstrual bleeding for 35 days) or amenorrhoea (i.e. no menstrual bleeding for > 6 months). Hirsutism was diagnosed by the presence of a self-reported mild or severe degree of visible hair growth, and hyperandrogenemia was diagnosed by the presence of a free testosterone (FT) level > 0.50 ng/dl. An LH:FSH ratio > 2 was classified as abnormal. Basal hormone levels [i.e. LH, FSH, testosterone, FT and sex hormone-binding globulin (SHBG)] were determined at Day 2 or 3 of a spontaneous or induced menstrual cycle and—in case of a hormonal treatment—prior to that therapy. Fasting insulin and glucose levels were also assessed. Biochemical analyses were performed at the laboratory of the Ghent University Hospital using the electrochemiluminescence immunoassay technique (Modular, Roche Diagnostics, Mannheim, Germany). Pre-pregnancy overweight was defined as a BMI of ≥ 25 kg/m² (WHO, 2010). All normal weight women had a pre-pregnancy BMI < 25 kg/m². The participant’s body weight and height were measured before the fertility treatment by using an electronic personal scale and a stadiometer, respectively, in order to calculate their BMI. The pre-pregnancy smoking behaviour was evaluated as present (i.e. at least one cigarette a day) or not (yes/no answer). It could not be determined whether the women who were known to be smokers, continued smoking or quit during pregnancy.

To study the pregnancy outcome, data on the presence of miscarriage, multiple pregnancy, hypertension during pregnancy, pre-eclampsia and diabetes during pregnancy were collected. A miscarriage was classified as a first or second trimester miscarriage when loss of the fetus occurred in the first 13 weeks of pregnancy or between 14 and 25 weeks of pregnancy, respectively. Since we had no data on blood pressure and the diabetic status of each woman before pregnancy, we used the term hypertension during pregnancy (HDP) and diabetes during pregnancy (DDP) instead of pregnancy-induced hypertension and GDM, respectively. Pre-eclampsia was diagnosed by the presence of hypertension during pregnancy (i.e. a blood pressure > 140/90 mmHg) and proteinuria > 300 mg/day. According to the guidelines of the American Diabetes Association, DDP was diagnosed at ~24 weeks of gestation using the oral glucose tolerance test (American Diabetes Association, 2014).
To study the delivery outcome, data on gestational age and mode of delivery were gathered. A gestational age of <32 weeks (starting from the first day of the last menstrual period) and between 32 and 37 weeks was classified as a very preterm birth and a preterm birth, respectively. The mode of delivery was observed as a variable with two categories, i.e. Caesarean section or vaginal delivery. The use of an epidural analgesia during a vaginal delivery was also registered.

Regarding the neonatal outcome, the birthweight was expressed in grams and a distinction was made between a low and a very low birthweight, representing a birthweight between 1500 and 2500 g or <1500 g, respectively. Macrosomia was diagnosed if birthweight was >4000 g. If children had adaptation problems, admission to a neonatal (intensive) care unit was also registered.

Ethical approval
This retrospective study was authorized by the Ethics Committee of the Ghent University Hospital. Informed consent from patients was not obtained but patient information was anonymized and de-identified prior to analysis.

Statistical analyses
Statistical analyses were performed using SPSS version 21.0. Independent samples t-tests, Mann–Whitney U, Chi-square and Fisher Exact tests were used where appropriate and were performed at the 5% significance level. The normal distribution of continuous variables was graphically inspected using QQ-plots. Univariate odds ratios (OR) and confidence intervals (CI) were based on small sample adjustments where needed (Jewell, 2003). Given the observational nature of the study, multiple linear and logistic regression was performed to adjust for confounding factors in all outcome analyses. In particular, the analyses of the miscarriage rate, the ongoing multiple pregnancy rate and the ongoing singleton pregnancy, delivery and neonatal outcomes were adjusted for age and pre-pregnancy smoking behaviour, since research has proved their negative influence on the perinatal outcome (Lowe et al., 1998; Delbaere et al., 2007; Cnattingius et al., 2013). The neonatal outcome parameters were additionally adjusted for gestational age (Land, 2006). Effects of overweight on neonatal outcome parameters must therefore be interpreted as reflecting the effects that cannot be explained by intermediate effects via gestational age. Adjusted odds ratios (AOR) and 95% CI were calculated for all outcome parameters and residual analyses confirmed the adequacy of the models.

Since multiple pregnancies have an important negative influence on perinatal outcome (The ESHRE Capri Workshop Group, 2000), we focused our analyses on the pregnancy, delivery and neonatal outcome of ongoing singleton pregnancies.

Table I Baseline characteristics of overweight versus normal weight women with polycystic ovary syndrome (PCOS).

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Overweight (n = 93)</th>
<th>Normal weight (n = 107)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>29 ± 4.2</td>
<td>28.4 ± 3.1</td>
<td>0.3</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>30.8 (27.7–33.5)</td>
<td>20.9 (20–22.3)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Smoking</td>
<td>22/93 (24.2%)</td>
<td>18/101 (17.8%)</td>
<td>0.3</td>
</tr>
<tr>
<td>Primigravida</td>
<td>70/93 (75.3%)</td>
<td>87/107 (81.3%)</td>
<td>0.3</td>
</tr>
<tr>
<td>PCOM</td>
<td>73/87 (83.9%)</td>
<td>96/105 (91.4%)</td>
<td>0.1</td>
</tr>
<tr>
<td>Irregular menstrual cycle</td>
<td>86/93 (92.5%)</td>
<td>103/107 (96.3%)</td>
<td>0.4</td>
</tr>
<tr>
<td>Hirsutism</td>
<td>38/64 (59.4%)</td>
<td>46/77 (59.7%)</td>
<td>1</td>
</tr>
<tr>
<td>LH:FSH ratio</td>
<td>1.5 (0.9–2.2)</td>
<td>1.6 (1–2.5)</td>
<td>0.4</td>
</tr>
<tr>
<td>Testosterone (ng/dl)</td>
<td>48.6 (38.5–61.9)</td>
<td>46.9 (34–62.6)</td>
<td>0.3</td>
</tr>
<tr>
<td>Free testosterone (ng/dl)</td>
<td>0.8 (0.6–1.1)</td>
<td>0.5 (0.4–0.8)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>SHBG (nmol/l)</td>
<td>33.6 (21.9–50.6)</td>
<td>62.1 (46.9–82.9)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Fasting insulin (µU/ml)</td>
<td>14 (7.8–22.5)</td>
<td>7.3 (4.7–10)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Treatment-to-pregnancy¹</td>
<td></td>
<td></td>
<td>0.4</td>
</tr>
<tr>
<td>Spontaneous pregnancy</td>
<td>11/93 (11.8%)</td>
<td>12/107 (11.2%)</td>
<td></td>
</tr>
<tr>
<td>Timed coitus</td>
<td>12/93 (12.9%)</td>
<td>21/107 (19.6%)</td>
<td></td>
</tr>
<tr>
<td>Intrauterine insemination</td>
<td>36/93 (38.7%)</td>
<td>39/107 (36.4%)</td>
<td></td>
</tr>
<tr>
<td>IVF/ICSI</td>
<td>34/93 (36.6%)</td>
<td>35/107 (32.7%)</td>
<td></td>
</tr>
<tr>
<td>Time-to-pregnancy² (months)</td>
<td>32 (20.3–49)</td>
<td>26 (17–36.5)</td>
<td>0.01</td>
</tr>
</tbody>
</table>

Continuous measurements are summarized as mean ± SD if symmetrically distributed, and as median (1st quartile–3rd quartile) otherwise. Nominal measurements are summarized as n (%).

PCOM, polycystic ovarian morphology; SHBG, sex hormone-binding globulin.

¹Treatment-to-pregnancy: the last treatment that has led to pregnancy.

²Time-to-pregnancy: the duration of the desire to have children.
<2 in both groups and this ratio was not significantly different between the overweight and normal weight women. There was a significant difference in the fT, SHBG and fasting insulin levels, as well as in the time-to-pregnancy. The fT level was significantly higher in the overweight group and the SHBG level was significantly lower in the overweight group. The fasting insulin level was only elevated in the overweight group.

### Perinatal outcome

In the overweight and normal weight group there were 22/93 (23.7%) and 25/107 (23.4%) miscarriages, resulting in 71 and 82 ongoing pregnancies, respectively (AOR 1, 95% CI 0.5–1.9, P = 0.9). All miscarriages, except one in the overweight group, were first trimester miscarriages. In both groups there were two ectopic pregnancies. The prevalence of ongoing multiple pregnancies was 8/69 (11.6%) in the overweight group and 9/80 (11.3%) in the normal weight group (AOR 0.9, 95% CI 0.3–2.7, P = 0.9). In each group one triplet pregnancy occurred.

Data on the pregnancy, delivery and neonatal outcome of ongoing singleton pregnancies in overweight and normal weight women are reported in Table II. No significant differences were detected in the prevalence of HDP and pre-eclampsia between the overweight and normal weight group. In one normal weight woman pre-eclampsia evolved to eclampsia. Despite the significant difference in fasting insulin levels between the two groups, there was no significant difference in prevalence of DDP. The age of the study participant was a significant predictor of the prevalence of DDP (P = 0.03), namely the older the participant, the more likely she was to develop DDP.

There was marginal evidence of a difference in gestational age between overweight and normal weight women (adjusted mean difference −4.8, 95% CI −9.7 to 0.1). The prevalence of preterm birth was significantly higher in overweight versus normal weight women. In the overweight group, one very preterm birth (25 weeks of pregnancy) occurred. With regard to the mode of delivery, there was marginal evidence of a difference in the prevalence of Caesarean sections versus vaginal deliveries between groups. Reasons for delivery through Caesarean section were fetal distress, a malpresentation, a narrowed pelvis and a prolonged labour. In the overweight group one Caesarean section was performed under general anaesthesia. An epidural analgesia was used otherwise.

There was a significantly higher birthweight in babies of overweight versus normal weight women, even after additional adjustment for gestational age (adjusted mean difference 259.4, 95% CI 83.4–435.4). We found no evidence of a higher prevalence of macrosomia in overweight versus normal weight women. In the overweight group, there was one newborn with a very low birthweight of 700 g due to a very preterm birth.

Since the study included one overweight woman with a very preterm birth (gestational age of 25 weeks) of a very low birthweight baby (700 g), a sensitivity analysis was performed by removing this case from the analysis of the pregnancy, delivery and neonatal outcome in ongoing singleton pregnancies. The exclusion of this study participant had no influence on the results.

We also performed a scenario analysis using the cut-off of 30 kg/m² instead of 25 kg/m² to evaluate the influence of obesity on the perinatal outcome in women with PCOS. The results showed marginal evidence of a higher prevalence of Caesarean sections versus vaginal deliveries in the obese group (AOR 0.4, 95% CI 0.2–0.9, P = 0.04) and of a difference in preterm birth between both groups (AOR 0.3, 95% CI 0.08–1, P = 0.05). All other results were similar to those of the original analysis.

### Discussion

The results of our study support the hypothesis that pre-pregnancy overweight in women with PCOS has—in addition to the negative effect of the syndrome in itself—a negative influence on the prevalence of...
Influence of overweight on perinatal outcome in PCOS

preterm birth and the birthweight of singletons. Marginal evidence is found of a shorter gestational age and a higher prevalence of Caesarean sections in ongoing singleton pregnancies of overweight versus normal weight women. No significant difference in miscarriage rate was observed between overweight and normal weight women.

Concerning the miscarriage rate, our results are the opposite of those in the retrospective cohort study by Fedorscak et al. (2000) investigating the influence of overweight (BMI $\geq 25$ kg/m$^2$) on the prevalence of early pregnancy loss in a sample of infertile women who received IVF or ICSI. They conclude that overweight was an independent risk factor for early pregnancy loss before 12 weeks of gestation (Fedorscak et al., 2000). A cohort study by Wang et al. (2001) found evidence that a pre-pregnancy BMI of 30–34.9 kg/m$^2$ has a significant negative and independent influence (AOR 1.79, 95%CI 1.16–2.75) on the prevalence of pregnancy loss before 20 weeks of gestation in women with PCOS.

Our findings suggest that pre-pregnancy overweight has a negative influence on the prevalence of preterm birth. A similar result was found by Cnattingius et al. (2013), studying the association between maternal obesity and the risk of preterm delivery in Swedish women using a retrospective design. These authors observed that obesity (BMI $\geq 30$ to $\geq 40$ kg/m$^2$) had a significant influence on the prevalence of preterm birth (gestational age <37 weeks) and this negative influence was highest in extremely preterm births (gestational age of 22–27 weeks). We cannot confirm this last statement because there was only one very preterm birth (gestational age of 25 weeks) in the overweight group, which was due to blood loss and preterm contractions. In contrast, the case–control study by Han et al. (2011) found no significant influence of overweight (BMI $>25$ kg/m$^2$) in women with PCOS on the prevalence of preterm birth. It has to be mentioned that these analyses were not adjusted for other important covariates.

In line with the conclusions of Han et al. (2011), our results showed that the birthweight of the newborn was significantly higher in overweight women in comparison to normal weight women. In contrast to Han et al. (2011), this result was only significant after adjustment for gestational age among others, which emerged as a significant predictor of birthweight. Our results thus express the direct effect of pre-pregnancy overweight on neonatal outcome, other than via gestational age, rather than the overall effect reported by Han et al. (2011).

Our findings do not confirm the existing evidence that overweight has an influence on the prevalence of macrosomia and GDM (Mikola et al., 2001; Turhan et al., 2003; Han et al., 2011). Although we did not find a significant difference in DDP, none of the normal weight women had DDP in comparison to 8.2% in the overweight group.

Although there is evidence that a treatment with IVF/ICSI has a negative influence on the prevalence of preterm birth in singleton pregnancies (Maman et al., 1998; Dhont et al., 1999), we could not confirm this since the treatment-to-pregnancy (i.e. the last treatment that has led to pregnancy) was not significantly associated with outcome in any of the analyses performed.

While we have adjusted for the confounding factors pre-pregnancy smoking behaviour and maternal age, a limitation of our study is that the comparison of overweight versus normal weight women with PCOS may be confounded by other, possibly unmeasured, factors. Caution is therefore warranted when interpreting all results as reflecting the influence of overweight. A further limitation is that our results for pregnancy, delivery and neonatal outcome can only be generalized to singleton ongoing pregnancies and that our analysis may also be vulnerable to selection bias due to the restriction to pregnant women who had experienced fertility problems. This restriction, while difficult to avoid, may induce bias as a result of the fact that pregnancy and fertility problems may themselves be influenced by overweight (Rosenbaum, 1984). For this reason the results may not be generalizable to the general PCOS community. Finally, because of the rather small sample size of ongoing singleton pregnancies ($n = 132$) and the resulting lack of power, non-significance of certain associations should not necessarily be interpreted as indicating the lack of association. A larger confirmatory study is therefore indicated, as well as a similar study looking into the influence of pre-pregnancy overweight in women with PCOS on the pregnancy, delivery and neonatal outcome in multiple pregnancies.

In our study, we focused on the influence of pre-pregnancy overweight rather than the gestational weight gain on perinatal outcome. In women without PCOS, gestational weight gain is also found to be an important predictor of perinatal complications (Bogaerts et al., 2012) and therefore an important factor to keep in mind during the medical supervision of pregnancy, delivery and post-partum. It would be interesting in the future to perform a prospective follow-up study looking into the difference in influence of pre-pregnancy BMI versus gestational weight gain on perinatal outcome in women with PCOS.

We conclude that pre-pregnancy overweight in women with PCOS has, in addition to the influence of the syndrome in itself, an important negative influence on the prevalence of preterm birth and the birthweight of the newborn singleton. Therefore we suggest the importance of pre-pregnancy weight loss in overweight women with PCOS in order to reduce the risk of adverse perinatal outcomes.

Authors’ roles

All authors have seen and approved the final version of this article. No author has conflicts of interest. V.D.F., researcher, has designed and executed the study, analysed and interpreted the data, drafted the manuscript and the critical discussion. S.V. has contributed to data analysis and interpretation, manuscript drafting and critical discussion. G.T. has contributed to data interpretation, manuscript drafting and critical discussion. J.G. has contributed to data interpretation, manuscript drafting and critical discussion. S.S. has contributed to data gathering and manuscript drafting. L.V. has contributed to data gathering and manuscript drafting. P.D.S., supervisor, has contributed to study design, study execution, data analysis and interpretation, manuscript drafting and critical discussion.

Funding

V.D.F. is holder of a Special PhD Fellowship by the Flemish Foundation for Scientific Research (FWO-Vlaanderen). P.D.S. is holder of a fundamental clinical research mandate by the Flemish Foundation for Scientific Research (FWO-Vlaanderen).

Conflict of interest

None declared.
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