Unexplained first trimester recurrent pregnancy loss and low venous reserves

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BACKGROUND: More than half of recurrent pregnancy loss (RPL) remains unexplained. We hypothesized that women with a history of unexplained RPL (URPL) have low venous reserve.

METHODS: Case–control study in 12 women with a history of URPL, 11 healthy nulliparous controls and 12 primiparous controls with a history of uncomplicated pregnancy. To quantify venous reserve, we measured plasma volume (PV, ml/m²) and venous compliance in forearm and calf (VCarm, VCcalf, (ml/dl)/mmHg) during the follicular phase of the menstrual cycle. Mean arterial blood pressure (mmHg) was measured by oscillometry. Arterial demand was evaluated by cardiac index (CI, (l/min)/m²).

RESULTS: Baseline characteristics were comparable between groups. All groups had similar CI. Women with a history of RPL had 14% and 9% lower mean PV compared with nulliparous and primiparous controls (P, 0.01 and P, 0.04, respectively). In women with URPL, the mean VCarm was 25% and 32% lower compared with nulliparous and primiparous controls (P = 0.04 and P, 0.01, respectively), while the mean VCcalf was 29 and 22% lower compared with the two control groups (P < 0.01 and P = 0.03, respectively).

CONCLUSIONS: Women with URPL have lower venous reserves when compared with controls at comparable arterial demand. Interventions that increase venous reserve may improve pregnancy outcome.

Key words: recurrent pregnancy loss / plasma volume / venous compliance / hemodynamic

Introduction

First trimester pregnancy loss affects up to 15% of clinically recognized pregnancies (Rai and Regan, 2006). Whereas most couples have successful subsequent pregnancies, 3% of the couples trying to conceive suffer from recurrent pregnancy loss (RPL) (Rai and Regan, 2006; Jaslow et al., 2010). The American Society for Reproductive Medicine (2008) redefined RPL in 2008 as two or more failed clinical pregnancies as documented by ultrasonography or histopathologic examination. Underlying conditions known to relate to RPL are anatomical uterine abnormalities, endocrine disorders, thrombophilia and chromosomal disorders. Nonetheless, even after extensive screening for these associated disorders, about half of RPL remains unexplained. This suggests that other, currently unknown, underlying factors are involved in RPL. Absence of an explanation for the recurrence contributes to depression and anxiety in women with RPL (Craig et al., 2002).

In women with RPL, the non-pregnant pulsatility index (PI) and the impedance in the uterine arteries are increased (Habara et al., 2002; Ferreira et al., 2007; Sikora et al., 2007). This pre-pregnancy circulatory profile reflects a high resistance to uterine flow. Women with a history of a pregnancy complicated by pre-eclampsia have comparable pre-pregnancy circulatory profile. In these formerly preeclamptic women, the non-pregnant PI in the uterine arteries inversely correlates with venous compliance which, in turn, correlates with plasma volume (PV) (Spaanderman et al., 2005). Along with venous compliance, PV represents the cardiovascular or, more specifically, the venous reserve capacity (Krabbendam et al., 2008b). Venous
reserve capacity represents the ability of the venous system to adapt to arterial demands. A mismatch between venous reserve capacity and arterial demands is known to correlate with adverse pregnancy outcomes, like fetal growth restriction (Spaanderman et al., 2005). Women diagnosed with RPL have a higher risk of vascular-complicated pregnancies in the next ongoing pregnancy (Weintraub et al., 2005; Trogstad et al., 2008; Trogstad et al., 2009). These findings suggest a common risk profile between women with RPL and women prone to develop pre-eclampsia or fetal growth restriction.

Based on these observations, we hypothesized that women with unexplained RPL (URPL) may have low pre-pregnancy venous reserve capacity, characterized by low PV and low venous compliance.

**Materials and methods**

We conducted an exploratory observational case–control study in 35 women. We compared 12 women with unexplained, not necessarily consecutive, RPL with two separate control groups. The first control group consisted of 11 healthy nulliparous women and the second control group included 12 healthy primiparous women, with a history of uncomplicated pregnancy. Women were matched for age and body mass index (BMI). Patients were recruited from the outpatient department of Obstetrics and Gynecology, Radboud University Nijmegen Medical Centre, Nijmegen, The Netherlands; controls were recruited by advertisement. URPL was defined as two or more pregnancy losses, clinically confirmed by elsewhere (Spaanderman et al., 2005). PV (ml/m²) was measured using the 125I-labeled albumin (125I-HSA) indicator dilution method as described elsewhere (Spaanderman et al., 2000; Krabbendam et al., 2009). Prior to the administration of the radioactive albumin, a venous blood sample was drawn to determine background activity as well as hemoglobin (mmol/l) and hematocrit (l/l) levels.

Taking 150 ml/m² difference in PV as clinically significant (α = 0.05, power 90%), based on previous finding of PV in healthy primiparous women, eight women are needed in each group (Scholten et al., 2011). For forearm venous compliance, to find a 0.02 ml/dl/mmHg difference as clinically important, at α = 0.05 and power 90%, based on previous findings, we needed to include 11 women in each group (Krabbendam et al., 2008a). We chose to include at least 11 subjects for each subgroup.

Statistical analysis was performed using Statistical Package for Social Sciences (SPSS) 16.0 (SPSS Inc., Chicago, IL, USA). All values are reported as means ± SD unless otherwise stated. Differences between groups were tested using one-way analysis of variance along with Bonferroni correction to correct for multiple testing. Kendall rank correlation coefficients

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**Reference**

Spaanderman, de Groot, and others. (2005). Venous reserve capacity represents the ability of the venous system to adapt to arterial demands. A mismatch between venous reserve capacity and arterial demands is known to correlate with adverse pregnancy outcomes, like fetal growth restriction. Women diagnosed with RPL have a higher risk of vascular-complicated pregnancies in the next ongoing pregnancy. These findings suggest a common risk profile between women with RPL and women prone to develop pre-eclampsia or fetal growth restriction.

Based on these observations, we hypothesized that women with unexplained RPL (URPL) may have low pre-pregnancy venous reserve capacity, characterized by low PV and low venous compliance.
between PV and venous compliance were calculated for each subgroup (URPL and nulliparous and primiparous controls, respectively) to compare correlations between groups. Pearson correlation coefficients were calculated to estimate correlation between PV and venous compliance in forearm and between PV and venous compliance in calf. The level of statistical significance was set at $\alpha = 0.05$.

### Results

We evaluated 12 women with URPL, 11 nulliparous controls and 12 primiparous controls between July 2009 and July 2010. Seven women had a history of two pregnancy losses, four women had three pregnancy losses and one woman had a history of four pregnancy losses at the time of evaluation. The median gestational age of ultrasound ascertainment or clinically evident pregnancy loss in patients was 10 weeks + 3 days (minimum: 7 weeks + 2 days; maximum: 16 weeks + 6 days). The mean interval between last pregnancy loss and cardiovascular evaluation was 27 ± 3 weeks. In primiparous controls, the mean interval between delivery and cardiovascular evaluation was 33 ± 4 weeks.

Subject characteristics did not differ between groups (Table I). Hemodynamically, women who were diagnosed with URPL differed from both control groups by higher mean pulse pressure, lower PV and lower venous compliance in both forearm and calf, while mean cardiac indices did not differ between groups (Table II). Pulse pressure was higher in women with URPL (50 ± 7 mmHg) compared with both nulliparous (44 ± 2 mmHg) and primiparous (43 ± 5 mmHg) controls ($P = 0.03$ and $P = 0.003$), respectively. PV in women with URPL was 14% lower compared with nulliparous controls (1407 versus 1633 ml/m$^2$, $P < 0.01$) and 9% lower compared with primiparous controls (1407 versus 1549 ml/m$^2$, $P = 0.04$). Mean PV did not differ between the two control groups ($P = 0.41$). Venous compliance in the forearm ($5.8 \times 10^{-2}$ (ml/dl)/mmHg) was lower in women with URPL when compared with both nulliparous ($7.6 \times 10^{-2}$ (ml/dl)/mmHg, $P = 0.04$) and primiparous controls ($8.5 \times 10^{-2}$ (ml/dl)/mmHg, $P < 0.01$). Calf venous compliance was also lower in women with URPL ($7.4 \times 10^{-2}$ (ml/dl)/mmHg) when compared with nulliparous ($10.4 \times 10^{-2}$ (ml/dl)/mmHg, $P < 0.01$) and primiparous controls ($9.6 \times 10^{-2}$ (ml/dl)/mmHg, $P = 0.03$), respectively. Mean venous compliance in both forearm and calf did not differ between the two control groups ($P = 0.72$ and $P = 0.89$, respectively). Kendall rank correlations between PV and forearm venous compliance in women with URPL were 0.38 ($P = 0.21$) and 0.42 ($P = 0.07$) in nulliparous controls and 0.42 ($P = 0.01$) in primiparous controls, respectively. Kendall rank correlations between PV and calf venous compliance in women with URPL were 0.12 ($P = 0.64$) and 0.13 ($P = 0.58$) in nulliparous controls and 0.33 ($P = 0.05$) in primiparous controls, respectively. Based on comparable correlation coefficients between subgroups, data were combined to calculate total correlation coefficients between PV and venous compliance. Total correlation coefficient ($r$) was 0.61 ($P < 0.01$) for the forearm and 0.52 ($P < 0.01$) for the calf (Fig. 1). All the individual data for PV and venous compliance are shown.

### Discussion

The major finding in the present exploratory study is a lower venous reserve capacity in women with URPL when compared with controls. At comparable arterial demands, as indicated by the CI, women who experienced URPL had lower mean PV and lower venous compliance in both forearm and calf when compared with both nulliparous and primiparous controls.

When women are systematically evaluated for possible underlying conditions after RPL, in 40–50% no etiologic factor is found. In an observational study of 1020 women with at least two pregnancy losses, an anatomical factor was found in 18%, a immunological factor in 17%, an endocrine factor in 8%, a thrombotic factor in 7% and a genetic factor in only 4% (Jaslow et al., 2010). Although parental genetic abnormalities may increase with increasing pregnancy losses, others demonstrated that the prevalence of abnormal results do not increase for most other abnormalities among women with different numbers of pregnancy losses (two, three or more) (Franssen et al., 2005; Jaslow et al., 2010).

Few studies have evaluated possible hemodynamic mechanisms in the pathophysiology of URPL. In these studies, the focus has always been on the arterial system. Previous studies demonstrated elevated uterine PI and flow wave velocity in women with URPL consistent with increased arterial stiffness (Habara et al., 2002; Ferreira et al., 2007). In our study, women with URPL demonstrated higher mean pulse pressure. Since the mean stroke volumes were comparable, this suggests lower arterial compliance, which is consistent with previous findings (Habara et al., 2002; Ferreira et al., 2007). With mean hemoglobin levels of 7.6 ± 0.4 mmol/l and no differences in hemoglobin levels between groups, severe anemia was excluded as an explanation for the increased arterial pulse pressure. Cardiac valve regurgitation is also an unlikely explanation in these young women. Loss of arterial compliance may also originate from increased sympathetic tone or reduced bioavailability of endothelium derived nitric oxide. Future studies are needed to elucidate these interactions.

Our study suggests a higher prevalence of reduced venous reserve capacity in women with URPL. In healthy persons, PV remains relatively constant as a result of tight regulation by the complex interaction between neurohormonal systems involved in sodium and water homeostasis (Kalra et al., 2002). Important mechanisms involved in the PV regulation are the sodium- and water-retaining effects of the renin–angiotensin–aldosterone system (RAAS), the diuretic effects of natriuretic peptides in response to atrial and ventricular wall stretch, and actions of the sympathetic nervous system (Kalra et al., 2002). The sympathic system acts on PV through a range of effects on both the kidneys and vasculature (Kalra et al., 2002); the latter in particular by acting on the functional venous capacitance. With comparable kidney functions between groups, our study indicates that the lower PV status in women with URPL unlikely results from markedly impaired kidney function.

The consequences of low PV for a subsequent ongoing pregnancy are currently unknown. A recent study demonstrated that in formerly preeclamptic women, a low pre-pregnancy PV relates to preeclampsia and fetal growth restriction in the subsequent pregnancy (Scholten et al., 2011). We speculate, in line with others (Burton and Jauniaux, 2004), that low venous reserve relates to restricted uterine perfusion that affects the uterine environment to such an extent that it influences embryonic, placental and uterine spiral artery development and may induce clinical entities such as RPL, hypertensive pregnancy and fetal growth restriction.
Early pregnancy is characterized by many important hemodynamic changes. Initially, there is a drop in vascular resistance. The exact mechanism for this drop in resistance is unknown. The resultant decrease in cardiac afterload reduces arterial blood pressure which is counteracted by a baroreceptor-mediated increase in CO and an increase in PV by RAAS activation (Duvekot et al., 1993; Duvekot and Peeters, 1994). Physiologically, PV increases by 10–15% within the first 12 weeks of gestation (Lund and Donovan, 1967; Whittaker and Lind, 1993; Bernstein et al., 2001). The resultant high flow, low resistance circulation of pregnancy is thought to be essential for healthy ongoing pregnancy. With further fetal development, adequate unstressed venous volume reserves are pivotal to meet the increasing uterine demands (Krabbendam et al., 2008b). Women with reduced venous reserves are less capable to mobilize venous volume in response to increased arterial demands (e.g. pregnancy, Krabbendam et al., 2008b, or exercise, Aardenburg et al., 2005), by which it can be insufficient for the fetus to develop. These women may need sustained increased sympathetic tone to meet the arterial demands of early pregnancy. Inadequate venous reserve capacity may then be detrimental and relate to both early and late pregnancy loss.

In contrast to many other factors associated with RPL, low venous reserve capacity is modifiable prior to a subsequent pregnancy. Aerobic exercise is known to induce PV expansion (Convertino, 1991; Sawka et al., 2000). This effect is initially established mainly through activation of the RAAS resulting in sodium retention. If training is continued, PV is further expanded through *de novo* protein synthesis, increasing oncotic intravascular pressure, by lowering of the sympathetic tone (Mueller, 2007) and increasing venous compliance (Krabbendam et al., 2009). Individuals who perform regular aerobic physical activity can increase their PV about 10% (Sawka et al.,

### Table I Characteristics of women with URPL and healthy nulliparous and primiparous controls with a history of uncomplicated pregnancy.

<table>
<thead>
<tr>
<th></th>
<th>URPL</th>
<th>Controls</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N</td>
<td>Nulliparous</td>
<td>Primiparous</td>
</tr>
<tr>
<td>N</td>
<td>12</td>
<td>11</td>
<td>12</td>
</tr>
<tr>
<td>Age (year)</td>
<td>32 ± 5</td>
<td>29 ± 4</td>
<td>32 ± 3</td>
</tr>
<tr>
<td>Height (cm)</td>
<td>170 ± 5</td>
<td>174 ± 4</td>
<td>171 ± 6</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>76 ± 10</td>
<td>74 ± 10</td>
<td>78 ± 11</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>26 ± 4</td>
<td>24 ± 3</td>
<td>26 ± 3</td>
</tr>
<tr>
<td>Day in follicular phase (day)</td>
<td>5 ± 2</td>
<td>5 ± 2</td>
<td>5 ± 2</td>
</tr>
<tr>
<td>Creatinine (µmol/l)</td>
<td>65 ± 7</td>
<td>71 ± 12</td>
<td>66 ± 9</td>
</tr>
<tr>
<td>Hemoglobin (mmol/l)</td>
<td>7.5 ± 0.4</td>
<td>7.4 ± 0.5</td>
<td>7.7 ± 0.8</td>
</tr>
<tr>
<td>Hematocrit (l/l)</td>
<td>0.35 ± 0.02</td>
<td>0.35 ± 0.02</td>
<td>0.37 ± 0.04</td>
</tr>
</tbody>
</table>

### Table II Hemodynamic variables in women with URPL and healthy nulliparous and primiparous controls with a history of uncomplicated pregnancy.

<table>
<thead>
<tr>
<th></th>
<th>URPL</th>
<th>Controls</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N</td>
<td>Nulliparous</td>
<td>Primiparous</td>
</tr>
<tr>
<td>N</td>
<td>12</td>
<td>11</td>
<td>12</td>
</tr>
<tr>
<td>Systolic blood pressure (mmHg)</td>
<td>115 ± 9</td>
<td>112 ± 5</td>
<td>108 ± 5</td>
</tr>
<tr>
<td>Diastolic blood pressure (mmHg)</td>
<td>65 ± 9</td>
<td>68 ± 6</td>
<td>67 ± 5</td>
</tr>
<tr>
<td>Mean arterial pressure (mmHg)</td>
<td>84 ± 9</td>
<td>81 ± 6</td>
<td>78 ± 4</td>
</tr>
<tr>
<td>Pulse pressure (mmHg)</td>
<td>50 ± 7&lt;sup&gt;a,b&lt;/sup&gt;</td>
<td>44 ± 2</td>
<td>43 ± 5</td>
</tr>
<tr>
<td>Stroke volume (ml)</td>
<td>79 ± 17</td>
<td>79 ± 16</td>
<td>75 ± 18</td>
</tr>
<tr>
<td>Heart rate (bpm)</td>
<td>62 ± 11</td>
<td>62 ± 8</td>
<td>60 ± 9</td>
</tr>
<tr>
<td>CO (l/min)</td>
<td>5.1 ± 1.1</td>
<td>5.2 ± 0.9</td>
<td>5.3 ± 0.7</td>
</tr>
<tr>
<td>CI ((l/min)/m²)</td>
<td>2.7 ± 0.6</td>
<td>2.8 ± 0.5</td>
<td>2.8 ± 0.4</td>
</tr>
<tr>
<td>Total peripheral vascular resistance (dyne s/cm⁵)</td>
<td>1379 ± 350</td>
<td>1271 ± 235</td>
<td>1195 ± 162</td>
</tr>
<tr>
<td>PV (ml/m²)</td>
<td>1407 ± 152&lt;sup&gt;a,b&lt;/sup&gt;</td>
<td>1633 ± 134</td>
<td>1549 ± 105</td>
</tr>
<tr>
<td>Venous compliance in forearm ((ml/dl)/mmHg)</td>
<td>5.8 ± 1.6 × 10&lt;sup&gt;-2&lt;/sup&gt;&lt;sup&gt;a,b&lt;/sup&gt;</td>
<td>7.6 ± 1.3 × 10&lt;sup&gt;-2&lt;/sup&gt;</td>
<td>8.5 ± 2.5 × 10&lt;sup&gt;-2&lt;/sup&gt;</td>
</tr>
<tr>
<td>Venous compliance in calf ((ml/dl)/mmHg)</td>
<td>7.4 ± 1.1 × 10&lt;sup&gt;-2&lt;/sup&gt;&lt;sup&gt;a,b&lt;/sup&gt;</td>
<td>10.4 ± 1.8 × 10&lt;sup&gt;-2&lt;/sup&gt;</td>
<td>9.6 ± 2.5 × 10&lt;sup&gt;-2&lt;/sup&gt;</td>
</tr>
</tbody>
</table>

<sup>a</sup> and <sup>b</sup> indicate significant difference compared with nulliparous and primiparous women, respectively. Control groups did not differ significantly.
2000). In this line of reasoning, women with RPL might benefit from aerobic exercise training through improvement of their cardiovascular reserve capacity.

This study population was modestly sized. We compared the hemodynamic profiles in women with URPL with nulliparous and primiparous control groups. The mean PVs of both control groups were similar and compare well with the PVs observed in a previous study in healthy women (Bernstein et al., 2003). Observing no differences in hemodynamic parameters between nulliparous and primiparous controls strengthens the idea that the two groups are an adequate representation of healthy controls. Future studies have to elucidate the contribution and impact of hemodynamic abnormalities in women with URPL and the possible beneficial effects of interventions aimed at improving these hemodynamic profiles.

In summary, women with URPL demonstrate reduced venous reserves when compared with healthy nulliparous and primiparous controls. Reduced venous reserve capacity is a potentially modifiable factor in the pathophysiology of RPL. Future research is needed to clarify the clinical relevance of reduced venous reserve capacity in women who experienced RPL.

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Authors’ roles

Janneke Donckers, MD: substantial contribution to conception and design, the acquisition of data, analysis and the interpretation of data, drafting the article and final approval of the version to be published. Ralph R. Scholten, MD: substantial contribution to conception and design, the acquisition of data, analysis and the interpretation of data, revising the article critically for important intellectual content and final approval of the version to be published. Wim J.G. Oyen, MD, PhD: substantial contribution to the acquisition of data, revising the article critically for important intellectual content and final approval of the version to be published. Maria T.E. Hopman, MD, PhD: substantial contribution to the acquisition of data, the interpretation of data, revising the article critically for important intellectual content and final approval of the version to be published. Fred K. Lotgering, MD, PhD: substantial contribution to conception and design, the interpretation of data, revising the article critically for important intellectual content and final approval of the version to be published. Marc E.A. Spaanderman, MD, PhD: substantial contribution to conception and design, the interpretation of data, revising the article critically for important intellectual content and final approval of the version to be published.

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Conflict of interest

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References


