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Resistin in pregnancy: Analysis of determinants in pairs of umbilical cord blood and maternal serum

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ABSTRACT

Objective: Despite intensive research on the cytokine resistin only few studies investigated mother-newborn-pairs during healthy pregnancy and reported about interactions with clinical obstetric variables or other cytokines. Comparison of existing studies is difficult due to differences between assays, sample collection, gestational age, definition of healthy controls and patient characteristics. Furthermore, differences between rodent models and humans do not allow for a direct comparison.

Methods: In this cross-sectional, prospective study 109 healthy mother-newborn pairs were analyzed. Maternal venous blood samples were taken on admission to the labor ward; newborn venous blood samples were drawn from the placental part of the umbilical cord (UC), immediately after clamping. Resistin, leptin, adiponectin, TNF-α, IL-6 and brain derived neurotrophic factor (BDNF) serum concentrations were measured with commercially available immunoassays. Determinants of maternal and newborn resistin levels were analyzed using simple and multiple linear regression.

Results: UC resistin levels were higher than maternal concentrations (median 17.69 ng/mL, IQR 7.36 vs. median 8.04 ng/mL, IQR 4.30). Correlation between UC and maternal resistin levels was moderate ($R = 0.503$, $p < 0.01$). In multiple regression analysis levels of maternal resistin and newborn TNF-α remained significant determining factors for UC resistin levels. Gestational age and maternal BDNF-levels remained significant factors for maternal resistin levels.

Conclusion: In healthy, term newborns and their respective mothers a positive correlation between maternal and newborn levels and an association with gestational age around term can be found and point to a placental source of resistin. Further investigations are needed to clarify the possible contribution of transplacental transport of resistin into the fetal circulation. Except for gestational age most of the clinical obstetric variables tested do not seem to be determining factors for fetal or maternal resistin. Interactions of resistin with other cytokines like TNF-α and BDNF could be the missing link for the conflicting results in literature.

1. Introduction

Within the past decade an increasing number of reports described a link between low-grade inflammation in obese and insulin-resistant patients and changes of inflammatory markers in early life, mediated through the placenta, with metabolic and cardiovascular diseases in offspring [1,2].

Resistin is a 12.5 kDa hexameric cytokine of 108 amino acids that promotes immune cell activation, chemotaxis, neutrophil extracellular trap formation and inflammatory cytokine production [3,4]. Resistin mRNA and its protein are found in numerous tissues [5] and both are expressed in placenta and amnion, mainly in syncytiotrophoblast. Resistin is thought to be secreted from the placenta into the maternal circulation [6,7] but the resistin receptor is unknown. Among others the

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Toll-Like Receptor 4 (TLR4) and adenyl-cyclase-associated protein 1 (CAP1) have been described to be a binding site and possible candidates mediating resistin functions [8–11]. The gene expression patterns of resistin differ considerably between rodents and humans [12,13]. While in rodents resistin is primarily secreted by adipocytes, human resistin is predominantly expressed by macrophages and peripheral blood mononuclear cells (PBMC) [14] its synthesis is induced by numerous factors, such as lipopolysaccharides (LPS), TNF-α, IL-6, IL-1ß, and resistin itself [15]. Human resistin is found in an oligomer and a trimer form, but the differences between both forms and their functions remain to be elucidated [4,16].

During pregnancy, resistin levels are significantly higher compared to non-pregnant controls [17,18]; a positive correlation with gestational age (GA), with a decline postpartum, has been observed [6,19–21]. Resistin has been suggested to modulate insulin sensitivity during pregnancy, however there is conflicting data [22–25]. Differences in GA, assay method, ethnicity, diagnostic criteria, as well as definitions of controls and interactions with other cytokines may account for the reported differences. Only few publications are present which report about interactions between resistin with other cytokines during pregnancy. Albeit in vitro studies describe an induction of resistin by TNF-α, studies in pregnant women [24,26] failed to show any correlation between the two cytokines. BDNF as well as resistin have been associated with the regulation/dysregulation of diabetes [4,27] but no studies reported on whether there is a dependence between the two.

Therefore, the aim of our study was to analyze resistin levels and determinants of umbilical cord (UC) resistin concentrations of healthy, term newborns and their respective mothers simultaneously with various other clinical variables and cytokines and to compare them with current data on resistin in pregnancy.

2. Material and methods

2.1. Data collection

This cross-sectional, prospective study was performed between December 2013 and April 2014 in the obstetric unit of a tertiary referral center. The study was part of a larger study, parts of which have been published [28–30]. Study design and consent forms were approved by the institutional ethics committee (number 269/13). All women gave their written informed consent.

2.2. Study population

Patients were recruited in the third trimester of pregnancy during their registration for delivery or on admission to labor ward. Cases with gestational age (GA) < 36 weeks, multiple pregnancy, and prenatally detected malformations were excluded. Baseline demographic and clinical data, antenatal history including pregnancy complications, obstetric, delivery and newborn data were obtained from the patients' charts and the departmental perinatal database.

2.3. Blood sample analysis

Maternal venous blood samples (6 mL) were taken on admission to the labor ward; newborn venous blood samples (6 mL) were drawn from the placental part of the umbilical cord, immediately after clamping of the cord, and before delivery of the placenta. All samples were transferred immediately after blood collection to +4 °C until centrifugation (4000 rpm, 10 min); thereafter, serum was separated and stored at −80 °C. Samples were thawed only once. Resistin, leptin, adiponectin, TNF-α, IL-6, and BDNF concentrations were measured in duplicate with a commercially available multiplex immunoassay (eBioscience, San Diego (USA)) according to the manufacturer's instructions. Adiponectin and leptin were measured in a TECAN reader (NANO Quant infinite M200 Pro, Switzerland) by direct sandwich ELISA kit (MERCK/Milipore, Germany). Measurements were conducted on a Luminex 200 Reader (Luminex, Austin, Texas, USA). A seven-point standard curve was generated on each plate for each analyte, and samples were interrogated with lower levels of detection of 6.01 pg/mL for resistin, 9.1 pg/mL for TNF-α, 9.1 pg/mL for IL-6, and 1.88 pg/mL for BDNF. Calculations were performed with Bio-Plex Manager 6.1 (Bio-Rad.Hercules CA, USA).

2.4. Statistical analysis

Descriptive statistics were used to present basic maternal and neonatal characteristics in the study population. The correlation between maternal and neonatal resistin levels was evaluated using Spearman's correlation coefficient. For continuous characteristics, the association of log-transformed maternal and neonatal resistin was analyzed using regression analysis. Comparisons of maternal and neonatal resistin levels for categorical variables were performed by analysis of variance or t-tests (if approximately normally distributed), otherwise Kruskall-Wallis- or Mann-Whitney-U-Test was used. Characteristics included: gravidity, smoking status, ethnicity, mode of delivery, type of analgesia, GA, body mass index (BMI) before pregnancy and at delivery, maternal conditions such as gestational diabetes (GDM), preeclampsia, maternal levels of leptin/resistin/TNF-α/IL-6/BDNF or newborn levels of leptin/resistin/IL-6/BDNF/TNF-α, birthweight, fetal sex, and umbilical artery pH. Multiple regression analysis included potentially promising characteristics (maternal: GA, umbilical artery pH, maternal BDNF, newborn resistin and newborn TNF-α; UC: GA, type of analgesia, umbilical artery pH, maternal BDNF, maternal resistin and newborn TNF-α) and adjustments for mode of delivery. For data analysis the statistical software package SPSS 20.0 (SPSS Inc., Chicago, Ill., USA) and SAS Version 9.4 (SAS Institute Inc., Cary, North Carolina, USA) was used.

3. Results

3.1. Baseline characteristics

One hundred and twenty women were recruited. Resistin immunoassay analysis failed in eight UC and three maternal specimens, leaving 109 maternal-newborn pairs.

Demographic, obstetric, and newborn data are listed in Table 1. With 5-minute Apgar scores ≥ 8 and umbilical artery pH ≥ 7.1 in the majority of the cases, the neonatal outcome was good. All newborns were healthy, in 15 mothers we recorded minor medical problems like treated hypothyreodism. Pregnancy complications were recorded in $n = 11$ (GDM) and $n = 4$ (preeclampsia). We did not find significant differences between the groups.

3.2. Correlation between fetal and maternal resistin

UC resistin levels were higher compared to maternal concentrations (median 17.69 ng/mL, IQR 7.36 vs. median 8.04 ng/mL, IQR 4.30). The correlation between UC and maternal resistin concentration was moderate ($R = 0.503$, $p < 0.01$) **(**Fig. 1**).**

Table 2 summarizes the results of the subgroup analysis. Both, maternal and UC resistin increased with advancing gestation (UC: $p = 0.043$; maternal blood: $p = 0.007$). Maternal and newborn resistin levels were positively correlated to GA ($r = 0.342$; $r = 0.277$; $p = 0.019$).

3.3. Simple linear regression analysis

Simple linear regression analysis showed the following significant **variables determining UC resistin** concentration including: maternal resistin concentration, UC pH, UC TNF-α concentration. There was no association with maternal levels of leptin/adiponectin/TNF-α /IL-6, or newborn levels of leptin/IL-6/BDNF/adiponectin.

Determinants of maternal resistin concentration included:

Table 1
Demographic, obstetric and newborn data (n = 109).

Demographic data	mean ± SD/n (%)
age (years)	33.9 ± 4.6
height (cm)	168.1 ± 6.9
BMI before pregnancy (kg/m^2) (median/IQR)	23.1 (6)
<25.0	72 (66.1)
25.0–29.9	19 (17.4)
30.0–34.9	10 (9.2)
>35.0	8 (7.3)
current smoker	6 (13.8)
white ethnicity	102 (93.6)
obstetric data	
parity (median/IQR)	1 (2)
gestational age at delivery (median/IQR)	38.9 (1.3)
weight gain during pregnancy (kg)	15 ± 5.4
BMI at delivery (kg/m^2) (median/IQR)	28.8 (5.7)
<25.0	11 (10.2)
25.0–29.9	54 (50.0)
30.0–34.9	24 (22.2)
>35.0	19 (17.6)
mode of delivery	
normal vaginal delivery	46 (42.2)
instrumental vaginal delivery	8 (7.3)
elective cesarean section	40 (36.7)
emergency cesarean section	15 (13.8)
analgesia/anesthesia	
no anesthesia, vaginal delivery	27 (24.8)*
regional anesthesia, vaginal delivery	27 (24.8)*
regional anesthesia, cesarean section	52 (47.7)§
general anesthesia, cesarean section	3 (2.8)§
EFW < 10. Percentile/IUGR	9 (8.3)
preeclampsia	4 (3.7)
diabetes in pregnancy	11 (10.1)
treated hypothyreoidism	15 (13.8)
Neonatal data	
male sex	50 (45.9)
birthweight (g)	3420 ± 483.3
birthweight percentile	
<10	9 (8.3)
10–90	88 (80.7)
>90	12 (11)
length (cm) (median/IQR)	51 (2.6)
head circumference (cm)) (median/IQR)	35.5 (1.4)
head circumference percentile	
<10	6 (5.5)
10–90	92 (84.4)
>90	11 (10.1)
ponderal index (kg/m^3) (median /IQR)	25.2 (2.6)
5 min. Apgar score ≥ 8	109 (100)
10 min. Apgar score ≥ 9	109 (100)
umbilical artery pH (median /IQR)	7.3 (0.8)
<7.10	1 (0.9)
7.10–7.19	17 (16.5)
7.20–7.30	42 (38.5)
>7.30	49 (45.0)

*: % of vaginal deliveries; §: % of cesarean sections; EFW: estimated fetal weight

maternal BDNF concentration, maternal and UC TNF-α concentration, level of UC resistin, and UC pH. There were no significant associations for: maternal leptin/adiponectin/IL-6, newborn leptin/IL-6/BDNF/adiponectin.

3.4. Multiple regression analysis

Maternal resistin (p = 0.0061) and newborn TNF-α (p = 0.0052) concentrations remained significant determining factors for UC resistin levels. For maternal resistin levels, GA and maternal BDNF levels remained significant factors. According to the fitted model and due to a reduced number of cases (UC TNF-α n = 91, maternal TNF-α n = 55) both seemed to be additional determining factors of maternal resistin.

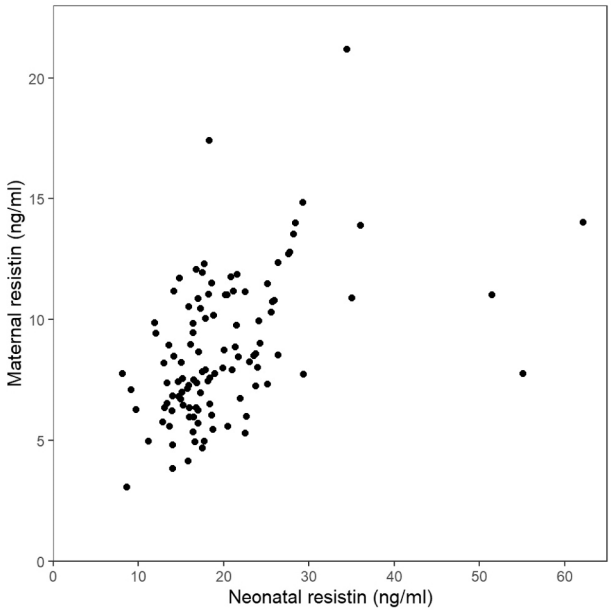

Fig. 1. Correlation between maternal and cord blood resistin levels (ng/ml); **(R = 0.503, p < 0.01).**

4. Discussion

Our study is the first to present resistin levels in a cohort of healthy mother-newborn pairs near term together with a broad spectrum of clinical obstetric variables and other cytokines. Except for gestational age most of the clinical obstetric variables tested were no determining factors for fetal or maternal resistin. Some facts have to be borne in mind for the subsequent discussion: Multiple variations between existing studies may account for the considerable differences in literature which make a comparison of results almost impossible. Type of sample, type of assay, GA, ethnicity, diagnostic criteria of subgroups (particularly in groups with GDM or preeclampsia) as well as the definition of controls are different between the studies. An additional complexity arises from lack of standardization of patented antibodies used in assays and the unit of measurement as a possible source of mistake.

4.1. Maternal and UC resistin levels

In our study UC resistin levels were higher compared to maternal concentrations; we found a positive correlation between UC and maternal resistin levels. Both, maternal and fetal resistin levels were also positively correlated to GA. To our knowledge, only four studies [7,17,31,32] provide information about maternal and UC resistin levels, our findings are in line with those studies. Cho et al. [7] described 37 mothers and their newborns in the third trimester. The authors suggested a secretion of resistin from the placenta into the fetal circulation since the molecular weight of 12.5 kDa precludes the passage of maternal resistin to the placenta without active transport. Similar data were presented by Cortelazzi et al. [17], who examined resistin levels of 73 pregnant women, 37 newborns at delivery and 3 fetal blood samples from chordocentesis between 20 and 41 weeks of pregnancy. Resistin was detectable in cord blood from 20 weeks of gestation, fetal levels were higher than maternal levels, and had a positive correlation with GA. In contrast to our findings, Cortelazzi et al. [17] did not find a correlation between maternal and fetal resistin levels. In the study of Solis-Paredes et al. [31] 76 mother-newborn pairs in the third trimester showed higher newborn resistin concentrations and a positive correlation to maternal resistin values. Of note, in 2016 Vernini et al. [32] described the data of 72 mother-newborn pairs in the third trimester. However, resistin concentrations were not mentioned and multiple

Table 2
Maternal and cord blood resistin concentrations (ng/ml), subgroup analysis (median/IQR).

	n	Resistin cord blood	Resistin maternal blood	n	p
overall	109	17.69 (7.36)	8.04 (430)	109	
gestational age					0.007
<37	18	16.58 (4.31)	7.07 (3.47)	18	
38–39	50	17.57 (6.30)	7.68 (3.10)	50	
≥ 40	41	20.15 (9.57)	10.07 (3.51)	41	
body mass index at delivery					n.s.
<25.0	11	18.53 (11.38)	8.54 (5.39)	11	
25.0–29.9	54	17.23 (6.35)	7.89 (4.34)	54	
30.0–34.9	24	18.56 (9.62)	8.62 (4.52)	24	
>34.9	19	17.85 (9.85)	8.04 (4.44)	19	
mode of delivery					n.s.
vaginal	54	18.06 (6.94)	8.83 (427)	54	
elective C/S	40	17.14 (6.55)	7.72 (254)	40	
emergency C/S	15	20.42 (8.67)	7.33 (396)	15	
analgesia/ anesthesia					
vaginal delivery					
none	27	18.53 (7.44)	9.47 (4.08)	28	n.s.
regional	27	17.83 (6.76)	8.49 (4.51)	28	
cesarean section					n.s.
regional	52	17.19 (6.62)	7.59 (2.73)	52	
general	3	24.11	9.95	3	
sex					n.s.
male	50	17.77 (7.43)	7.85 (4.55)	50	
female	59	17.46 (7.72)	8.26 (4.26)	59	
birth weight percentile					n.s.
<10	9	16.76 (8.80)	6.35 (5.67)	9	
10–90	88	17.76 (7.92)	8.13 (4.12)	88	
>90	12	17.35 (7.20)	8.19 (3.51)	12	
head circumference percentile					n.s.
<10	6	19.64 (7.25)	6.78 (7.02)	6	
10–90	92	17.57 (7.48)	8.02 (4.17)	92	
>90	11	20.15 (7.86)	8.25 (2.76)	11	
current smoker					n.s.
no data	9	17.25 (4.29)	10.07 (4.48)	9	
yes	6	17.14 (4.32)	6.68 (3.48)	6	
no	94	18.24 (7.95)	8.12 (4.26)	94	
gestational diabetes					n.s.
yes	11	15.70 (7.82)	7.59 (4.02)	11	
no	98	17.84 (6.86)	8.14 (4.32)	98	
preeclampsia					n.s.
yes	4	22.07 (7.79)	10.57 (4.71)	4	
no	105	17.67 (7.27)	8.00 (4.24)	105	
hypothyreosis					
yes	15	20.80 (9.82)	8.84 (2.37)	15	
no	94	19.73 (8.00)	8.75 (3.03)	94	n.s.

C/S, cesarean section.

regression analysis was only described with respect to maternal and perinatal outcome parameters.

The positive correlation between newborn and maternal levels and its association with GA point to the placenta as a contributing factor to maternal and fetal levels. Further investigations are needed to clarify whether there is an active transport of resistin across the placenta into the fetal circulation and to what extent it contributes to the fetal and neonatal concentration.

4.2. Gestational age

In our study group, maternal and UC resistin levels increased between week 37 and 41 and showed a significant correlation to GA near term. Data concerning GA are conflicting. Cortelazzi et al. [17] found a positive correlation of UC resistin and a negative correlation of maternal levels with GA. Cho et al. [7] found no correlation of both and Nien et al. [19] reported an increase of maternal resistin towards term, but no significant differences between the groups of different trimesters.

The longitudinal analysis of Vitoratos et al. [20] used only maternal resistin levels and showed an increase of resistin from the second towards the third trimester and a decrease in the postpartum period, but significant differences were only seen in women with GDM. In contrast to this study, Noureldeen et al. [21] described a significant increase of maternal resistin concentration according to GA in 142 pregnant women between 21 and 33 weeks of gestation, but without a difference in the GDM group. Larger longitudinal analyses in healthy mothers are needed to create reference values of maternal and fetal-neonatal resistin levels according to GA.

4.3. Tumor necrosis factor α (TNF-α)

Only few publications are present which report about interactions between resistin with other cytokines during pregnancy. In our study, UC TNF-α remained a significant determining factor for UC resistin levels after stepwise regression analysis. According to the fitted model and due to a reduced number of cases (UC TNF-α n = 91, maternal TNF-α n = 55) both seemed to be additional determining factors of maternal resistin. Besides that, we did not find a correlation with leptin, adiponectin or IL-6. In contrast to our results, Haugen et al. [24] did not find a correlation between maternal plasma resistin and TNF-α levels. Lappas et al. [26] incubated maternal blood, placenta, fetal membranes, adipose tissue and skeletal muscle with TNF-α, but did not find an effect on resistin release, and accounted this finding to the concentration needed to elicit a response. Our findings are in line with studies in non-pregnant patients, describing a direct interaction of both cytokines: Patel et al. [33] found that circulating resistin levels correlate with CRP, TNF-α, IL6 levels in the general population. Human resistin is induced by inflammatory stimuli as TNF-α, IL-6, IL-ß1, resistin itself and lipopolysaccharides (LPS) in vitro [15] and resistin upregulates the expression of proinflammatory cytokines such as TNF-α, IL-6, IL-12, monocyte chemoatractant protein (MCP) in PBMCs via nuclear factor kappa B (NFKB) pathway [34]. Lehrke et al. [35] described that endotoxemia induced a dramatic increase in resistin in primary human macrophages and LPS induced TNF-α which preceeded the increase in resistin in their study.

4.4. Brain derived neurotrophic factor (BDNF)

BDNF is a neurotrophin that plays an important role in the central nervous system. Several reports documented an association with different inflammatory conditions, and BDNF protein as well as its receptors were found not only in the brain but also in peripheral tissues and placenta [36]. Inflammation plays a key role in insulin resistance and diabetes, and both BDNF and resistin have been associated with the regulation/dysregulation in this condition [4,27]. Moreover, different studies demonstrated an increase of BDNF levels and amelioration of glucose metabolism with antidiabetic drugs like metformin or glimepiride [37] whereas Steppan et al. [38] showed that circulating resistin levels are decreased by the anti-diabetic drug rosiglitazone. Lappas et al. [26] found an biphasic effect of insulin on resistin release from placenta and described insulin as a key regulator of resistin gene expression. And McTernan et al. [39] described that insulin stimulated resistin secretion in adipocytes in a concentration-dependent manner in vitro, but found no correlation between plasma resistin and insulin. There are several studies showing a key role of BDNF in energy homeostasis and insulin sensitivity in humans [27]. Whereas resistin and its association to

obesity, diabetes and insulin sensitivity have been studied intensively but with conflicting results during recent times. To our knowledge this is the first study to show that levels of maternal BDNF remained a significant determining factor for maternal resistin levels after stepwise regression. We can only speculate about the opposite relationsship between BDNF and resistin, but suggest it as a missing link concerning the conflicting data of resistin and insulin resistance.

4.5. Resistin in gestational diabetes and preeclampsia

We did not find any correlation of UC or maternal resistin levels with GDM or preeclampsia. Despite several investigations about the association between resistin and GDM or preeclampsia there is still conflicting data. Variations in GA at sample collection, differences in ethnicity, assay methods, severity and diagnostic criteria of GDM are given as explanation. Our results support the findings of the metaanalyses by Lobo et al. [22] and Bellos et al. [40] which did not find an association of GDM with maternal resistin levels among the majority of 29 studies between 2008 and 2018. In contrast, the metaanalysis of Hu et al. [23], which analyzed 18 studies with 1041 cases and 1292 controls according to GA at sampling found an association between the risk of GDM and serum resistin concentrations in the third trimester.

Although in non-pregnant patients resistin is predictive of atherosclerosis and poor outcomes in cardiovascular diseases and seems to be strongly associated with hypertension [12], data about resistin and hypertension during pregnancy are still conflicting. Cortelazzi et al. [17] found lower resistin levels in preeclamptic patients, whereas Haugen et al. [24] and Song et al. [25] found higher levels, and Hendler et al. [41] no differences between patients with or without preeclampsia, or between groups with mild or severe forms.

5. Limitations

Our study has several limitations: besides the fact that knowledge about resistin functions and its receptor(s) is still lacking; likewise, reference values according to GA and knowledge whether there is active transport between maternal and fetal compartments is lacking. Furthermore, due to differences in the timing of the sample collection between mother (before birth) and newborn (after birth) and the lack of knowledge about possible determinants during parturition we cannot exclude the act of parturition as a confounding factor. Moreover, the number of patients with pregnancy complications in our study group was small.

6. Conclusion

Our study is the first to present resistin levels in a cohort of healthy mother-newborn pairs near term together with a broad spectrum of clinical obstetric variables and other cytokines. Except for gestational age most of the clinical obstetric variables tested were no determining factors for fetal or maternal resistin. The positive correlation between fetal and maternal levels and its association with GA confirm other studies and suggest a placental source of resistin. Further investigations are needed to build fetal and maternal reference values and clarify the possible contribution of transplacental transport of resistin into the fetal circulation. Interaction of resistin with other cytokines like TNF-α and BDNF could be the missing link for the conflicting results in literature.

CRediT authorship contribution statement

Anne Floeck: Conceptualization, Methodology, Validation, Formal analysis, Investigation, Writing - original draft. **Nina Ferrari:** Investigation, Resources. **Christine Joisten:** Conceptualization, Methodology, Investigation, Resources. **Maria T. Puth:** Validation, Formal analysis, Writing - review & editing. **Brigitte Strizek:** Validation, Investigation, Resources, Writing - review & editing. **Ramona Dolscheid-Pommerich:** Writing - review & editing. **Ulrich Gembruch:** Investigation, Resources, Writing - review & editing. **Waltraut M. Merz:** Conceptualization, Methodology, Investigation, Resources, Writing - original draft.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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