

# Intrauterine growth restriction in a cohort of migrants in Germany

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## Research article

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# Abstract

**Background:** Migrant women may have an increased risk of adverse birth outcomes. This study analyses the occurrence of low birth weight, preterm birth and intrauterine growth restriction (IUGR) in pregnant migrants.

**Method:** Cross-sectional study of 82 mother-child pairs of pregnant migrants attending medical care in Germany.

**Results:** Median age was 27 years, 49% were of oriental-asian ethnicity and median year of migration was 2015. At least one previous pregnancy was reported in 76%. Delivery mode was caesarian section in 40%. Median gestational age was 39.7 weeks. Preterm birth occurred in 6.1%. Median gestational age for preterm birth was 32.3 weeks. Low birth weight (<2500 g) occurred in 6.1%. Birth weights below the 10th percentile of birth weight for gestational age were observed in 8.5% of the total cohort.

**Conclusions:** Compared to German data no increased occurrence of low birth weight, preterm birth or IUGR was found. Of note, rate of caesarian section was higher than in the general population for reasons yet to be identified. The authors propose stratification according to migration status for the national documentation of birth outcomes in Germany.

Trial registration: ClinicalTrials.gov, NCT03158298. Registered 18 May 2017 - Retrospectively registered, <https://clinicaltrials.gov/ct2/show/NCT03158298>

## 1. Background

The idea of intrauterine growth restriction (IUGR) was introduced in 1961 by Warkany et al. to describe the relationship between gestational age and birth weight [1]. In the more recent literature intrauterine growth restriction (IUGR), fetal growth restriction (FGR) and small for gestational age (SGA) are frequently used synonymously. It is defined as the incapability of a fetus to achieve expected growth – usually with birth weight below the 10th percentile for gestational age [2, 3]. It is expected to occur in 5–10% of all pregnancies [4] and can be compared across multi-ethnic populations [5].

Migration to Europe is a hot topic and the European Community (EU) is facing the greatest influx of refugees and migrants since the Second World War [6]. A recent study by Dopfer et al. analyzed a cohort of 2911 migrants in Germany. Within this cohort, the proportion of women of childbearing age was 18%. The authors analyzed the frequency of pregnancy among all women of fertile age and revealed a relevant pregnancy rate of  $9.1 \pm 0.8\%$ . The most common country of origin of pregnant migrants was Syria (51.1%) followed by Afghanistan (21.3%) [7].

Older international studies on birth outcomes in migrant populations show heterogeneous results. A systemic review from 2010 describes that south-central Asians were more likely to have low birth weight deliveries after migration to the US and Europe, while women from Sub-Saharan Africa, Latin-America

and the Caribbean were more likely to have low birth weight deliveries in Europe only [8]. The birth outcomes evaluated in this review were low birth weight (less than 2500 g) and preterm birth (gestational age < 37 weeks). A population-based study from Belgium, which examined more than 1.3 million births between 1998 and 2010, found an increased risk of perinatal mortality in all migrant groups. Low birth weight (less than 2500 g) was not observed in the whole study population. However, the subgroup analysis showed that children born to mothers from Sub-Saharan Africa had a significantly higher risk of LBW compared to Belgians [9]. The more precise definition for IUGR/FGR/SGA, which reflects the relationship between gestational age and birth weight using birth weight percentiles, was not used in either studies. A systematic review published in 2017 identified only three studies in the US and Europe, respectively, to investigate newborn risk for adverse birth outcome for this endpoint. The European studies were conducted in Scandinavia (two in Sweden and one in Denmark) [10].

To the best of our knowledge this is the first publication from Germany that investigates the frequency of adverse birth outcomes in a migrant cohort from African and Oriental Asian countries targeting FGR, defined as birth weight below the 10th percentile of the reference curves, as primary endpoint.

## **2. Methods**

We conducted a prospectively ascertained cross-sectional study using mother-child data pairs in pregnant migrants attending medical care in Germany. Recruitment phase was 18 month (March 2017 to September 2018). The study was registered with the US national library of medicine (ClinicalTrials.gov Identifier: NCT03158298).

### **2.1 Inclusion criteria**

Pregnant women > 18 years who migrated to Germany from Africa or the Middle East and gave written informed consent to the study (see supplementary file 1).

Exclusion criteria

Placental pathology due to any cause and any other medical condition affecting fetal growth.

### **2.2 Assessments**

A questionnaire was completed on each subject including demographics, age, medical history. Data concerning the primary (birth weight percentiles) and secondary outcomes (FGR, stillbirth and premature delivery) were collected. The necessary values consisted of gestational age, weight and sex of the new born. Gestational age was either determined by ultrasound or by calculation of the last menstrual period (see supplementary file 2).

### **2.3 Questionnaire**

Data was collected with a standardized case report form (eCRF) and pseudonymised at source.

Categorical variables were: smoking, alcohol, diabetes, baby gender, ethnic origin and parity. Continuous

variables were birth weight, gestational age, maternal height and weight [11]. The country of origin provided the ethnic origin more precisely. Medical conditions and concomitant medication of the mother were documented. Relevant laboratory parameters - if available from the clinical routine – were added to the dataset: Hemoglobin, Eosinophils, HIV-status and Hepatitis B and C status (Hbs-Ag, Anti-HCV) (see supplementary file 2).

## 2.4 Ethics statement

The study was reviewed and approved by the Ethical Committee of the University Hospital Jena, Germany (approval # 4629-12/15, see supplementary file 3). Follow votes were obtained for study sites in Berlin, Munich, Halle and Walsrode. All women signed an informed consent in their national language allowing the use of their data and serum sample for scientific purposes. The study was registered with the US national library of medicine (ClinicalTrials.gov Identifier: NCT03158298).

## 2.5 Statistical analysis

The statistical evaluation of the data was carried out with using SPSS Statistics Version 25. The data were first assessed for normal distribution using the Kolmogorov-Smirnov test. For normally distributed metric data the t-test was used for independent variables and for non-normally distributed metric data the Mann-Whitney-U-test was used. The  $\chi^2$  test was used for the analysis of nominal or ordinary data. A p-value of  $< 0.05$  (\*) was considered to be significant. Birth percentiles for height, weight and head circumference were calculated according to Voigt et al. [12]. In the univariate regression model, known and unknown factors that could influence the birth weight percentile were evaluated. Individual confounders with a potential influence, which had a p-value  $< 0.05$  in the univariate linear regression model, were checked for multicollinearity using Kendall-Tau-B correlation analysis and included in the multiple linear regression analysis if no correlation ( $r < 0.5$ ) was present. The results of the multiple linear regression analysis were considered valid if the Durbin-Watson value was between 1 and 3, Variance Inflation Factor (VIF) was  $< 5$ , the largest condition index was  $< 30$  and  $p < 0.05$ .

## 3. Results

### 3.1 Study population

82 mother-child data pairs were included. Patients were recruited multicentric in Germany (Jena (n = 35) 42.7%, Walsrode (n = 21) 25.6%, Halle (n = 13) 15.9%, Munich (n = 8) 9.8% and Berlin (n = 5) 6.1%).

Table 1  
Characteristics of migrant women and their migration route

Total number of cases	n = 82	
Age [years; median (IQR)]	27 (11.0)	
Weight [kg; median (IQR)]	67.5 (25.0)	
BMI [kg/m <sup>2</sup> ; median (IQR)]	24.42 (7.89)	
Year of migration to Europe; median (IQR)	2015 (2.0)	
Ethnicity [n (%)]	Oriental Asian	40 (48.8)
	African	23 (28.0)
	Caucasian	14 (17.1)
	other	5 (6.1)
Most frequent countries of origin [n (%)]	Syria	29 (35.4)
	Somalia	10 (12.2)
	Nigeria	9 (11.0)
Transportation during migration [n (%)] (multiple answers possible)	by car	16 (19.5)
	foot	20 (24.4)
	by airplane	39 (47.6)
	by boat	22 (26.8)
	train	22 (26.8)

The demographic characteristics of migrant women and details of the migration route are shown in Table 1. Most frequent countries of origin were Syria (35.4%) and Somalia (12.2%). Migration from African countries was observed in 40 cases (48.8%) and from Oriental Asian countries in 42 cases (51.2%).

## 3.2 Medical history

The medical history included smoking in 3.7%, 1.2% ex-smoker and non-smoker in 95.1%. Alcohol consumption was reported monthly or less in 4.9% and never in 95.1%. In 1.2% and 3.7% hypertension and diabetes were reported, respectively. In 8% previous anemia was evident.

## 3.3 Laboratory values

Median hemoglobin was 6.98 mmol/l (IQR 1,40). HIV status was unknown/not analyzed in 53.7%, negative in 45.1% and one woman reported to be HIV positive. Hepatitis B was negative for 91.5% and unknown/not analyzed in 8.5%. Hepatitis C was negative for 17.1% and unknown/not analyzed in 82.9%.

## 3.4 Previous pregnancies

75.6% of the investigated women reported at least one previous pregnancy. 82% of all previous pregnancies resulted in live births, 16% in abortions and 2% in stillbirths.

## 3.5 Current pregnancy

Gestational diabetes was reported in 8.5% and pregnancy-induced hypertension in 2.4%. Pre-eclampsia occurred in 1.2%. Median weight of the mother at delivery was 78 kg (IQR 18.5). Concomitant medications during pregnancy were magnesium and methyldopa in 9.8% and 4.9%. Acetylsalicylic acid and metoprolol were not observed. Other medication was reported in 26.8%.

## 3.6 Perinatal/neonatal outcomes

The newborn was male in 52%. The delivery mode was in 57.3% spontaneous and in 2.4% assisted vaginal delivery. Primary caesarean section and secondary caesarean section were performed in 18.3% and 22%, respectively. Median gestational age was 39.71 weeks (IQR 2.43). Newborns length was in median 51 cm (IQR 3.0). Median for birth weight and head circumference were 3318 g (IQR 623) and 35 cm (IQR 2.0). Median for placental weight was 500 g (IQR 105.0). Median Apgar after five and ten minutes was 10 (IQR 1 and 0). Admission to NICU was reported in 21%. No newborn deceased. Median umbilical cord pH was 7.29 (IQR 0.14). Preterm birth (< 37 week) occurred in 5 cases (6.1%). Median gestational age for preterm birth was 32.3 weeks (IQR 6.5). Low birth weight (< 2500 g) occurred in 5 cases (6.1%). 4 of those were preterm at the same time. Median weight for low birth weight was 1700 g (IQR 1265). Median percentile for weight was 35.0 (IQR 37.25). Median percentile for height was 38 (IQR 40.00) and median percentile for head circumference was 42.5 (IQR 41.25). Birth weight below the 10th percentile of birth weight for gestational age were observed in 8.5% (n = 7) of the total cohort. However, there was no preterm birth (< 37 week) below 10th percentile of birth weight for gestational age. Gender-specific analysis showed a difference between female (4.7%) and male (12.8%) newborns (5 vs. 2). However, the gender difference was not significant (p = 0.25). This results in the observation of fetal growth restriction (> 10% below the 10th birth weight percentile) for newborn boys in our migrant population.

Univariate regression models for the birth weight percentile outcome revealed significant influence of: mother's height, mother's weight at delivery, transport to Europe by foot, transport to Europe by boot, number of previous pregnancies and number of previous birth (p ≤ .05 for all).

In the multiple linear regression models with the factors transport to Europe by foot, number of previous births and mother's weight at delivery, a quality of 0.30 (adjusted R-square) was achieved. The results of the analysis are shown in Table 2. A significant positive effect could be demonstrated for all three factors (each p < .01). Transport to Europe by foot and number of previous births turned out to be equally strong (both standardized regression coefficients are 0.28 and 0.27) whereby weight at delivery with beta = 0.33 shows a comparatively higher value. The non-standardized regression coefficients B show the change in the dependent variable in one step change in the factor. If the weight of the mother at delivery increases

by one unit (kilograms), the birth weight percentile increases by 0.56 units (percentiles). I.e. if the weight increases by 2 kg on delivery, the birth weight is one percentile higher. The same applies vice versa: if the weight of the mother on delivery drops by 2 kg, the birth weight is one percentile lower. If the number of previous births increases by one unit, the birth weight is 5.8 percentiles higher. The reverse applies again when the number of previous births is one unit lower. If the transport to Europe was by foot (nominal variable), the birth weight was 16.1 percentiles higher than for migrants who used another means of transport.

Table 2

Influence of various independent variables on birth weight percentiles - Results of the multiple linear regression models

Multiple linear Regression		Transport to Europe by foot	Number of previous births	Weight at delivery
Dependent variable: Birth weight percentile				
Non-standard coefficients	Regression coefficient B	16.084	5.803	0.545
	Standard Error	5.607	2.152	0.163
standard coefficient	Beta	0.278	0.271	0.333
Significance	p	0.005	0.009	0.001
95.0% Confidence intervals for B	lower limit	4.910	1.515	0.220
	upper limit	27.258	10.091	0.869
Collinearity statistics	VIF	1.018	1.097	1.079

## 4. Discussion

Perinatal outcomes for Germany are published for 2016 and 2017 with more than 700.000 datasets per year. Unfortunately, these data were not stratified for migration background or nationality. Compared with the Germany-wide context, the data from our cohort are not noticeable different for FGR (8.5%) and preterm birth (6.1%). Overall preterm birth in Germany occurs in 6.6% and 10% of newborns are small for gestational age, i.e. below the 10th percentile of birth weight. Surprisingly FGR is even somewhat rarer in our cohort than in a national comparison. However, the caesarean section rate in our cohort (40%), is remarkably higher than in the overall German data (30%). Whereas the combined endpoint of FGR and premature birth in Germany occurs in 10% but does not occur in our migrant cohort [13].

The quality of our data is underlined by the results of the regression analysis, where known positive factors influencing the birth weight are confirmed (previous births and mothers weight at delivery). The significantly positive influence of transport to Europe by foot on birth weight percentiles remains an inexplicable observation. We actually expected a reversely significant result and debated better physical training condition of the mothers due to the positive physical strain of long walking distances in the past.

Data on birth outcomes of the migrant population currently entering Europe are rare, and for Germany in particular, no data are available up to now. Only three European publications reflect the relationship between gestational age and birth weight to measure the frequency of adverse birth outcomes in migrant populations. Li et al. investigated more than 1 million births in Sweden from 1982 to 2006. The authors found that 4.1% of newborns born to non-Swedish mothers met the criteria for SGA, compared to 3.3% in the Swedish population [14]. In Denmark, Pedersen et al. conducted a similar analysis from 1978 to 2007 and found that migration was related to SGA rather than preterm births. The risk difference for newborns from Somalian women was 70.1% (CI 62.2 to 77.9) [15]. The third Scandinavian study compared 262 newborns of mothers from Somalia with 523 babies born in Sweden. The risk for SGA was almost three times higher in the Somalian babies (OR 2.95 CI 1.49 to 5.82). The emergency caesarean section rate was almost twice as high (OR 1.90 CI 1.16–3.10) with an approximately five-fold increased risk before the onset of labor (OR 4.96, CI 1.73–14.22) [16].

Our study was conducted in a cross sectional setting without a comparison group. We found fetal growth restriction in 8.5% of the investigated population. Compared to the results of Li et al. with data from 1982 to 2006, FGR was twice as common in our cohort (8.5% vs. 4.1%) and newborn boys were more likely to be small for gestational age (boys 12.8% vs. 4.7%). Previous studies did not differentiate by gender [14].

Taking into account that one third of our study population migrated from Syria in 2015, it can be assumed that the sequelae of war and the circumstances of forced migration entails consequences in the most vulnerable population group. This could explain why we found the prevalence of FGR twice as high as reported by Li et al. in 2012. On the other hand, our data are surprising compared to the German population, because they correspond to the national average both in terms of FGR and in terms of prematurity. However, the comparison of the Swedish data from 2012 with German data from 2016/2017 suggests that FGR is less common in the naïve-Swedish population than in Germany. However, the data from Germany do not include a delimitation of births of women with a migration background compared to births of naïve mothers, but are a mixture of all births in 2016/2017.

While comparing the migrant specific data from Scandinavia with our cohort the assumed increase in negative birth outcomes in migrant populations should prompt us to reconsider medical strategies for refugees in Germany, and pregnant refugees should receive particular medical attention to protect the most vulnerable group from further health damage. Especially in view of the high rate of caesarean sections in the Scandinavian study of women from Somalia (OR up to 5fold) and our secondary section rate of 22%, we should consider that we might not guide migrant women sufficiently through birth possibly due to a lack of communication which could eventually support spontaneous vaginal delivery [16]. However, a scientific comparison of our data with a more recent data set from other European countries would be appreciated. In addition, we propose stratification according to migration status for the national documentation of birth outcomes in Germany.

## 5. Conclusions



Compared to German data no increased occurrence of low birth weight, preterm birth or IUGR was found. Of note, rate of caesarian section was higher than in the general population for reasons yet to be identified. We propose stratification according to migration status for the national documentation of birth outcomes in Germany.

## Abbreviations

BMI

body mass index

CI

confidence interval

eCRF

electronic case report form

EU

European Community

FGR

fetal growth restriction

HCV

hepatitis C virus

HIV

human immunodeficiency virus

IUGR

intrauterine growth restriction

IQR

interquartile range

LBW

low birth weight

NICU

Neonatal intensive care unit

OR

Odds-Ratio

SGA

small for gestational age

US

United States

VIF

Variance Inflation Factor

## Declarations

## **Ethics approval and consent to participate:**

The Study was approved by the Ethics Committee of the University Hospital Jena (File number: 4629-12/15). All patients were asked to give written consent to participate in the study (see supplementary file 3).

## **Consent for publication:**

Not applicable

## **Availability of data and materials:**

The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.

## **Competing Interest:**

None for all authors

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## **Authors' contributions:**

The study was conceived and designed by BTS and AJ. Patients were recruited by TG, SM, GS, CPDC and VS. Data analysis and statistics was conducted by JA. The Manuscript was drafted by BTS and CD and critically corrected by KvW, SML and MWP. All authors have read and approved the manuscript

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Not applicable

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