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Cohort profile: Targeted antenatal screening for haemoglobinopathies in Basel

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Cohort profile: Targeted antenatal screening for haemoglobinopathies in Basel

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Abstract

Purpose: The pregnancy cohort was established to examine the prevalence and the variety of haemoglobinopathies in high risk group of pregnant women.

Participants: The pregnancy cohort is located in the Department of Obstetrics and Antenatal Care, University hospital of Basel. The pregnant women were recruited in the first trimester between June 2015 and May 2019. Family origin questionnaires were used to screen pregnant women for the risk for haemoglobinopathies. According to this questionnaire pregnant women were divided into two groups: women with high risk and women with low risk for haemoglobinopathies. In women with high risk red blood cell indices, iron status and chromatography were conducted.

Findings to date: There were 1785 pregnant women on recruitment. Out of 1785 women, 929 were identified as high risk group. Due to missing data in 74 pregnant women with high risk, further analysis was conducted in 855 women. The prevalence of haemoglobinopathies in high risk group was 14.5% (124/855).

Future plans: This cohort will be used to: 1) implicate the screening in prenatal care in Basel; 2) recommend the screening among pregnant women with high risk of haemoglobinopathies in Switzerland; 3) improve prenatal and neonatal care in patients with haemoglobinopathies; 4) examine adverse pregnancy outcomes in
women with haemoglobinopathies; 5) reduce the maternal and neonatal morbidity and mortality in the future.
Strengths and limitations of this study

- For the first time to our knowledge, a prospective study has been conducted to examine the prevalence and the variety of haemoglobinopathies among pregnant women in Switzerland.

- The limitation of our study is the absence of conducting of high-performance liquid chromatography and molecular analysis in all women. However, conducting universal screening would not be cost effective in low risk pregnant women.

- The prevalence of 14.5% in high risk group of pregnant women confirms an increasing significance of screening for haemoglobinopathies in this group of patients.

- Our findings provide new insights into the prevalence of haemoglobinopathies and have important implications in health service of Switzerland.
Introduction

Haemoglobinopathies are among the most common inherited disorders worldwide. As recommended by the World Health Organisation (WHO), screening and genetic counselling for haemoglobin disorders should be an intrinsic part of health care in most counties (1). Two factors have recently highlighted the need for a more coordinated approach to diagnosis and management of haemoglobinopathies. The globalisation of migration flows has increased cultural diversity, bringing to Europe populations from areas with a high prevalence of haemoglobinopathies, and increasing the number of patients (2-6).

In the publication “A Roadmap for European Haematology Research” (7), the European Haematology Association (EHA) in 2017 recommended undertaking detailed epidemiological studies in all countries, particularly in Western Europe, as a prerequisite for the implementation of effective prevention programmes. Different policies for the antenatal and neonatal screening for haemoglobinopathies have been adapted in Europe and the data on the number of affected patients are not available for every country (8). A few countries with evidence of increasing numbers of patients have not yet considered planning national strategies (8).

Microcytic hypochromic anaemia as a result of the combination of ineffective erythropoiesis within the bone marrow, peripheral haemolysis of red cells within
the circulation, and impaired globin synthesis leads to impaired oxygen transport and diminished tissue oxygenation because of limited haemoglobin-oxygen binding (9). On the other side, high iron stores, impaired biorheology, increased adhesion-mediated vaso-occlusion, and haemolysis-mediated endothelial dysfunction explain the potential adverse effect of haemoglobinopathy on pregnancy outcomes (10). Increasing migration in Switzerland, growing importance of early laboratory diagnosis as well as missing data on prevalence of haemoglobinopathies in Switzerland, targeted screening for haemoglobinopathies in pregnant women has been started at the University hospital of Basel since 2015.
Cohort description

A prospective, cross sectional study was conducted at the University hospital of Basel, Department of Obstetrics and Antenatal Care between June 2015 and May 2019. Pregnant women were recruited in the first trimester in our outpatients’ department. Family origin questionnaires were used to screen pregnant women for the risk for haemoglobinopathies in the first trimester.

The Family origin questionnaire was adopted from the National Health Screening: Sickle Cell and Thalassaemia Screening Programme in England. According to this questionnaire pregnant women were divided into two groups: women with high risk and women with low risk for haemoglobinopathies.

In women with high risk red blood cell indices, iron status and high-performance liquid chromatography (HPLC) were conducted. For women identified as carriers, their partner was tested for haemoglobinopathy irrespective of family origin. In the case of a suspicion for alpha thalassaemia based on haematological parameters, the molecular analysis was performed. If they were both carriers of haemoglobinopathies, genetic counselling was recommended and an antenatal genetic testing via choriovillous sampling or amniocentesis was discussed. Although, since the discovery of cell-free foetal DNA in maternal plasma, the non-invasive prenatal assessment of haemoglobinopathies has been achieved.
Inclusion criteria were age $\geq 18$ years and gestational age at recruitment between 11 and 14 of gestational weeks. The primary outcome was the prevalence of haemoglobinopathies in pregnant women. Secondary outcome measures included the variety of haemoglobinopathies, the prevalence of anaemia, iron deficiency anaemia and iron deficiency.

**Haematological Assessment**

Blood samples were collected by venepuncture. All blood measurements (blood count, CRP, ferritin and HPLC) were conducted at the University Hospital of Basel, Department of Laboratory Medicine. Screening for anaemia in pregnancy is general recommended in Switzerland including the red blood count and ferritin ad the end of the first trimester (11).

Haemoglobin (Hb), red blood cell count (RBC), haematocrit (HCT), mean corpuscular volume (MCV), mean corpuscular haemoglobin (MCH), hypochromic red blood cells (HRC) and red blood distribution width (RDW) were measured using a haematology analyser. Mean corpuscular haemoglobin was automatically calculated from Hb and RBC.
Serum ferritin was assessed by chemiluminescence immunoassay and CRP was assessed by immunoturbidimetry. The haemoglobins were separated and processed by high-performance liquid chromatography.

**Study criteria**

According to current guidelines based on recommendations of the CDC (Centre for Disease Control, USA), anaemia in pregnancy was defined by a Hb of less than 110 g/l in the first trimester (12). Iron deficiency was defined as a serum ferritin <30 µg/l. Iron deficiency anaemia was defined by a Hb of less than 110 g/l and serum ferritin <30 µg/l. Anaemia of other aetiology was defined by a Hb of less than 110 g/l and serum ferritin ≥30 µg/l.

The determination of HbA2 (>3.5%) was indicative of beta thalassaemia (13). In some cases of beta thalassaemia confirmation by molecular analysis were conducted. In haemoglobinopathy S the presence of Hb S was confirmed, in haemoglobinopathy E the presence of Hb E and in haemoglobinopathy C the presence of Hb C. Alpha thalassaemia was diagnosed when results of iron status, HbA2 and Hb F levels were normal but there was microcytosis with either erythrocytosis and mild anaemia, or normal RBC count with minimal anaemia.
Anaemia of other aetiologies was mainly caused by haemoglobinopathies, diseases of the liver or kidney, HIV infection, antiphospholipid syndrome etc.

Statistical analysis was conducted using STATA 12.0 (Stata Corporation College Station, TX). Blood indices, CRP and serum ferritin were expressed as mean ± standard deviation (s.d.) and range, or median and range.

**Ethics and dissemination**

The study received ethical approval from the local ethics committee in Basel (ID 2019-01065). It was registered under [http://www.ClinicalTrials.gov](http://www.ClinicalTrials.gov) (NCT04029142) in July 2019. All members of the research team are aware of the guidelines for good clinical practice.

The findings of this study will be published in a peer-reviewed journal, and presented at national scientific conferences, to disseminate the results to academic and health professional audiences, and made available to participants and to a wider public on our website at the time of publication.

**Data sharing**

After publication of the study individual anonymous participant data including variable keys will be available upon request by the corresponding author.
Researchers may request data to repeat the analyses or use the data for secondary analyses (e.g. systematic review and meta-analysis).

**Patient and public involvement**

Patients and the public were neither involved in developing the hypothesis, the specific aims or the research question, nor were they involved in developing plan for design or implementation of the study.
Findings to date

There were 1785 pregnant women on recruitment. Out of 1785 women, 929 were identified as high risk group. Due to missing data in 74 pregnant women with high risk, the analysis was conducted in 855 women (Figure 1). The mean gestational age at screening was 12.3 ± 2 weeks. The mean of haemoglobin was 121 ± 13 (68-174 g/l) and the median of ferritin 40 µg/l (4-5607 µg/l) (Table 1). There were 139 anaemic women (139/855; 16.3%); namely iron deficiency anaemia was identified in 75 women (75/855; 8.8%) and anaemia of other aetiology in 64 women (64/855; 7.5%) (Figure 2). There were 242 women with iron deficiency (242/855; 28.3%). The mean of haemoglobin, serum ferritin and CRP of each group are in Table 2. According to the origin mostly pregnant women on the screening came from Africa (mostly Eritrea), Turkey, India and Middle East (mostly Syria).

The prevalence of haemoglobinopathies was 14.5% in high risk group of women (124/855) and 6.95% in all group (124/1785). There were 23 women with sickle cell anaemia, 39 with alpha thalassaemia, 42 with heterozygous beta thalassaemia, 12 with other haemoglobinopathies and 8 with compound haemoglobinopathy (Table 3). The mean of haemoglobin was 111 ± 14 (79-162 g/l) and the median of ferritin 54 µg/l (5-5607 µg/l). 48 women with haemoglobinopathies were anaemic (48/104; 46.2%) and 56 were non-anaemic (56/104; 53.8%) (Figure 3). In 33
women with haemoglobinopathies, anaemia of other reasons was diagnosed (33/104, 31.7%) and in 15 iron deficiency anaemia in the first trimester (15/104; 14.4%) (Figure 3). There were 33 women with haemoglobinopathy and concomitant iron deficiency; in 71 pregnant women with haemoglobinopathy was the ferritin $\geq$ 30 µg/l. In 12 women was the ferritin $\geq$ 150 µg/l (12/104; 11.5%), namely in 2 women with alpha thalassaemia, in 6 with beta thalassaemia and in 4 with homozygous sickle cell anaemia. There was very low mean of MCV and MCH in the group of women with alpha and beta thalassaemia (the mean of MCV was 70 ± 7 fl [59-88] and MCH 23 ± 3 pg [16.3-31.6]). In 23 pregnant women (23/124) haemoglobinopathy was diagnosed previously and in 101 women on the basis of our screening (101/124).


**Discussion**

Population movements affect the distribution of inherited disorders of haemoglobin within countries, with previously isolated populations increasingly interacting and large numbers of migrants moving from rural to urban areas, and the complexity of genotypes which can be observed, as newly introduced variants can interact with local ones to create more or less severe phenotypes (14).

The prevalence of haemoglobinopathies of 6.95% (124/1785) in total in our study group corresponds to an overall average of 8% (15). In high risk group of women, the prevalence of haemoglobinopathies was twice as high (124/855; 14.5%). Using the family origin questionnaire we identified a group of pregnant women with haemoglobinopathies which might otherwise have been overlooked. Half of the pregnant women with haemoglobinopathies were non-anaemic and two-thirds of them had normal iron status in the first trimester. One third of women with haemoglobinopathies showed anaemia with normal iron status in the first trimester. The majority of pregnant women on screening came from Africa, Turkey, Middle East and India. Due to political changes we reported significantly more women from Syria and Eritrea in the last years.

In UK, where there is a well-established linked neonatal and antenatal screening programme for haemoglobinopathies, a downward trend in reported screen-positive
results is discernible in some areas (8). In contrast, Germany, Italy and France have recently been accepting large numbers of refugees and have faced a dramatic increase in their patient numbers since 2014 (8). Except for Belgium, UK, Cyprus, Greece, Germany and Spain, there exists no national registry for haemoglobinopathies in European countries (8). According to the Organisation for Economic Co-operation and Development, the percentage of foreign-born populations within the European Union in 2008 ranged from 4% in Finland to 37% in Luxembourg (15). Switzerland has one of the highest proportions of foreigners in its midst among all nations 24.6% in 2016 (15).

European countries with a high prevalence of haemoglobinopathies have adopted a neonatal screening programme (France, Belgium, the Netherlands, Spain), an early antenatal screening programme (Sweden, Italy), linked neonatal and antenatal screening programme (UK), or preconceptional, premarital screening programme (Cyprus, Greece, Turkey). Antenatal screening programmes are generally assessed by the uptake of prenatal diagnosis, optimal management care, and/or allow the termination of affected pregnancies.

The limitation of our study is the lack of HPLC in all women. However, conducting universal screening would not be cost effective in low risk pregnant women. The choice of the screening method is based on cost-effectiveness, and it has been
demonstrated that at a prevalence of at least 16 sickle cell traits/1,000 there is no significant cost difference between universal and targeted screening programmes. Therefore, targeted antenatal screening is recommended in Switzerland. On the other side, it could be impossible to detect women with sickle cell trait by using the full blood count alone for screening because of normal red cell blood parameters in these patients.

Our findings will be used to: 1) implicate the screening in prenatal care in Basel; 2) recommend the screening among pregnant women with high risk of haemoglobinopathies in Switzerland; 3) improve prenatal and neonatal care in patients with haemoglobinopathies; 4) examine adverse pregnancy outcomes in women with haemoglobinopathies; 5) reduce the maternal and neonatal morbidity and mortality in the future.
Contributors GAB is the principal investigator who designed the study, carried out the quantitative analysis and drafted the article. FG collected the data. IH reviewed and edited the manuscript. All authors read and approved the final manuscript.

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Competing interests None declared.

Patient consent for publication Not required.

Data availability statement Data are available on reasonable request.
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Table 1.

Haematological data and serum iron status (n=855).

| Parameter          | Value                  |
|--------------------|------------------------|
| Hb (g/l)           | 121 ± 12.7 (68-174)    |
| RBC (x10^6/µl)     | 4.18 ± 0.45 (2.2-6.2)  |
| MCV (fl)           | 84.5 ± 7.4 (59-122.2)  |
| MCH (pg)           | 24.2 ± 3.7 (19.2-32.9) |
| HRC (%)            | 0.8 (0-58.2)           |
| RDW (%)            | 14.2 ± 1.9 (11.7-32.1) |
| Reticulocytes (%)  | 18.5 ± 5.1 (7-38)      |
| Ferritin (µg/l)    | 40 (4-5607)            |
| CRP (mg/l)         | 4.1 (0.3-89.9)         |
Table 2.

The haematological data of the four groups (n=855).

Group 1: normal (474); group 2: ID (242); group 3: IDA (75); group 4: anaemia of other reason (64).

|                      | Group 1 |       | Group 2 |       | Group 3 |       | Group 4 |       |
|----------------------|---------|-------|---------|-------|---------|-------|---------|-------|
|                      | Mean (SD) | Range | Mean (SD) | Range | Mean (SD) | Range | Mean (SD) | Range |
| **Hb (g/l)**         | 125 (8.1) | 110-155 | 124 (8.5) | 110-148 | 100 (8.1) | 75-109 | 100 (8.4) | 68-109 |
| **Median**           |          |       |          |       |          |       |          |       |
| **CRP (mg/l)**       | 3.9 | 0.3-89.9 | 4 | 0.3-141 | 5.4 | 1-27.6 | 5.1 | 1.2-19.4 |
| **Ferritin (μg/l)**  | 62 | 30-436 | 19 (6.6) | 5-29 | 14 (6.5) | 4-27 | 73.5 | (30-827) |
Table 3.

The variety of haemoglobinopathies.

| Haemoglobinopathy                                      | Number of patients (%) |
|--------------------------------------------------------|------------------------|
| Beta thalassaemia                                      | 42 (33.9)              |
| Alpha thalassaemia                                     | 39 (31.5)              |
| - Heterozygous                                         | 27                     |
| - Homozygous                                           | 12                     |
| Sickle cell anaemia                                    | 23 (18.5)              |
| - Heterozygous                                         | 18                     |
| - Homozygous                                           | 5                      |
| Other haemoglobinopathies                              | 12 (9.7)               |
| - Heterozygous Delta thalassaemia                      | 3                      |
| - Haemoglobinopathy E                                  | 6                      |
| - Heterozygous haemoglobinopathy C                     | 1                      |
| - Heterozygous haemoglobinopathy D                     | 2                      |
| Compound Haemoglobinopathy                             | 8 (6.4)                |
| - Heterozygous sickle cell anaemia/                    | 4                      |
| heterozygous alpha thalassaemia                        |                        |
| - Heterozygous sickle cell anaemia/                    | 1                      |
| homozygous alpha thalassaemia                          |                        |
| - Homozygous sickle cell anaemia/                       | 1                      |
| heterozygous alpha thalassaemia                        |                        |
| - Heterozygous haemoglobinopathy C/                    | 1                      |
| homozygous alpha thalassaemia                          |                        |
| - Heterozygous haemoglobinopathy E/                     | 1                      |
| heterozygous alpha thalassaemia                        |                        |
Figure 1.

Pregnant women on screening, on testing and completion.
Figure 2.

Allocation of pregnant women with high risk of haemoglobinopathy according to haemoglobin and serum ferritin.

n = 855

Anaemic women
n = 139 (16.3%)

Iron deficiency anaemia
n = 75 (8.8%)

Anaemia of other reason
n = 64 (7.5%)

Non-anaemic women
n = 716 (83.7%)

Iron deficiency
n = 242 (28.3%)

Normal
n = 474 (55.4%)
Figure 3. Allocation of pregnant women with haemoglobinopathy according to haemoglobin and serum ferritin.

Pregnant women with Haemoglobinopathy  
\( n = 124 \)

Uncompleted data  
\( n = 20 \)

On analysis  
\( n = 104 \)

Anaemic women  
\( n = 48 \ (46.2\%) \)

Iron deficiency anaemia  
\( n = 15 \ (14.4\%) \)

Anaemia of other reasons  
\( n = 33 \ (31.7\%) \)

Non-anaemic women  
\( n = 56 \ (53.8\%) \)

Iron deficiency  
\( n = 18 \ (17.4\%) \)

Normal  
\( n = 38 \ (36.5\%) \)
Cohort profile: Targeted antenatal screening for haemoglobinopathies in Basel

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Cohort profile: Targeted antenatal screening for haemoglobinopathies in Basel

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Competing interests: None declared.
Abstract

Purpose: The pregnancy cohort was established to examine the prevalence and variety of haemoglobinopathies in a high-risk group of pregnant women.

Participants: The pregnancy cohort is located in the Department of Obstetrics and Antenatal Care, University Hospital of Basel. The pregnant women were recruited in the first trimester between June 2015 and May 2019. Family origin questionnaires were used to screen pregnant women for the risk of a haemoglobin variant. Based on the questionnaire, pregnant women were divided into two groups: women with a high-risk and women with a low risk of a haemoglobin variant. In women with a high-risk, red blood cell indices, iron status and chromatography were conducted.

Findings to date: 1785 pregnant women were recruited. Out of the 1785 women, 929 were identified as part of the high-risk group. Due to missing
data in 74 pregnant women with a high-risk, the final analysis was conducted in the remaining 855 women. The prevalence of haemoglobinopathies in the high-risk group was 14.5% (124/855).

**Future plans:** This cohort will be used to: 1) implement the screening in prenatal care in Basel; 2) recommend the screening among pregnant women with a high-risk of a haemoglobin variant in Switzerland; 3) improve prenatal and neonatal care in patients with a haemoglobin variant; 4) examine adverse pregnancy outcomes in women with a haemoglobin variant; 5) reduce maternal and neonatal morbidity and mortality in the future.
Strengths and limitations of this study

- For the first time, to our knowledge, a prospective study has been conducted to examine the prevalence and the variety of haemoglobinopathies among pregnant women in Switzerland.

- The limitation of our study is the lack of conducting of a high-performance liquid chromatography and molecular analysis in all women. However, conducting a universal screening would not be cost effective in low risk pregnant women.

- The prevalence of 14.5% in the high-risk group of pregnant women confirms an increasing significance of screening for haemoglobinopathies in this group of patients.
- Our findings provide new insights into the prevalence of haemoglobinopathies and have important implications in the health service within Switzerland.
Introduction

Haemoglobinopathies are among the most common inherited disorders worldwide. As recommended by the World Health Organisation (WHO), screening and genetic counselling for haemoglobin disorders should be an intrinsic part of health care in most counties (1). Two factors have recently highlighted the need for a more coordinated approach to diagnosis and management of haemoglobinopathies. Firstly, the globalisation of migration flows has increased cultural diversity, bringing to Europe populations from areas with a high prevalence of haemoglobinopathies, and secondly, there is an increasing the number of patients requiring health services (2-6).

In the publication “A Roadmap for European Haematology Research” (7), the European Haematology Association (EHA) in 2017 recommended undertaking detailed epidemiological studies in all countries, particularly in
Western Europe, as a prerequisite for the implementation of effective prevention programmes. Since then different policies for the antenatal and neonatal screening for haemoglobinopathies have been adapted in Europe, yet the data covering affected patients are not available to every country (8). There are a few countries with evidence of increasing numbers of patients; however, planning national strategies of increasing number of patients has not been considered at this time to the best of our knowledge (8). Although haemoglobinopathies have increased significantly in Switzerland in recent years, there is no routine prenatal and/or neonatal screening for haemoglobinopathies. Therefore, since 2015 we have been conducting targeted prenatal screening at the University Hospital of Basel to investigate the current prevalence of haemoglobinopathy and improve prenatal care in these patients.
Cohort description

A prospective, cross sectional study was conducted at the University Hospital of Basel, Department of Obstetrics and Antenatal Care between June 2015 and May 2019. Pregnant women were recruited in the first trimester from our outpatients’ department. Family origin questionnaires were used to screen pregnant women for the risk of haemoglobinopathies in the first trimester.

The Family origin questionnaire was adopted from the National Health Screening: Sickle Cell and Thalassaemia Screening Programme in England (Figure 1). Based on the questionnaire, pregnant women were divided into two groups: women with a high-risk and women with a low risk of haemoglobinopathies.
In women with a high-risk, red blood cell indices, iron status and high-performance liquid chromatography (HPLC) were conducted. For women identified as carriers, their partner was also tested for haemoglobinopathy, irrespective of family origin. In cases where alpha thalassaemia was suspected based on haematological parameters (MCH< 27 pg regardless of iron status) (9), a molecular analysis was performed. If both were carriers of haemoglobinopathies, genetic counselling was recommended and an antenatal genetic testing via chorioc villous sampling or amniocentesis was discussed with the patient.

Inclusion criteria were: patients aged ≥ 18 years and having a gestational age at recruitment between 11 and 14 weeks. The primary outcome was the prevalence of haemoglobinopathies in pregnant women. Secondary outcome
measures included a variety of haemoglobinopathies, the prevalence of
anaemia, iron deficiency anaemia and iron deficiency.

**Haematological Assessment**

Screening for anaemia in pregnancy is generally recommended in
Switzerland, including the red blood count and ferritin at the end of the first
trimester (10). Therefore, blood samples were collected by venepuncture. All
blood measurements (blood count, CRP, ferritin and HPLC) were conducted
at the University Hospital of Basel, Department of Laboratory Medicine.

Haemoglobin (Hb), red blood cell count (RBC), haematocrit (HCT), mean
corpuscular volume (MCV), mean corpuscular haemoglobin (MCH),
hypochromic red blood cells (HRC) and red blood distribution width (RDW)
were measured using a haematology analyser. The mean corpuscular
haemoglobin was automatically calculated from Hb and RBC counts.

Haematological parameters were measured using an ADVIA haematology analyser system (Bayer Diagnostics, Leverkusen, Germany).

Serum ferritin was assessed by chemiluminescence immunoassay and CRP was assessed by immunoturbidimetry. The haemoglobins were separated and processed by a high-performance liquid chromatography using a model-II machine from Company Bio-Rad.

**Study criteria**

Based on the guidelines from the CDC (Centre for Disease Control, USA), anaemia in pregnancy was defined as an Hb of less than 110 g/l in the first trimester (11). Iron deficiency was defined as a serum ferritin of less than 30
µg/l. Iron deficiency anaemia was defined as an Hb of less than 110 g/l and serum ferritin of less than 30 µg/l. Anaemia of other aetiology was defined as an Hb of less than 110 g/l and serum ferritin 30 µg/l or more.

The determination of HbA2 (≥3.5%) was indicative of beta thalassaemia (9, 12). In some cases of beta thalassaemia (borderline elevated HbA2 and in cases where both partners are carriers for beta thalassaemia), confirmation by molecular analysis was conducted. Haemoglobin variants (haemoglobin C, D, E, F, S) were identified using HPLC technique. A sickle solubility test was performed whenever haemoglobin S was detected by HPLC.

A genetic test was performed in women with MCH < 27 pg to confirm alpha thalassemia (9). Two forms of alpha thalassaemia trait were described, the homozygous alpha trait if the missing genes are on opposite chromosomes
and the heterozygous alpha trait if both missing genes are on the same chromosomes.

Anaemia of other aetiologies was found to be primarily caused by haemoglobinopathies, diseases of the liver or kidney, HIV infection, antiphospholipid syndrome and so on.

Statistical analysis was conducted using STATA 12.0 (Stata Corporation College Station, TX). Blood indices, CRP and serum ferritin were expressed as mean ± standard deviation (s.d.) and range, or median and range.

Ethics and dissemination

The study received ethical approval from the local ethics committee in Basel (ID 2019-01065). It was registered under [http://www.ClinicalTrials.gov](http://www.ClinicalTrials.gov)
(NCT04029142) in July 2019. All members of the research team were aware of the guidelines for good clinical practice.

The findings of this study will be published in a peer-reviewed journal and presented at national scientific conferences to disseminate the results to academic and health professional audiences. In addition, they will be made available to the participants and to the wider public on our website at the time of publication.

**Data sharing**

After publication of the study individual, anonymous participant data, including variable keys, will be available from the corresponding author on request. Researchers may request data to repeat the analyses or use the data for secondary analyses (e.g. systematic review and meta-analysis).
Patient and public involvement

The patients and the public were neither involved in developing the hypothesis, the specific aims or the research question, nor were they involved in developing the plan for design or implementation of the study.
Findings to date

In brief, 1785 pregnant women were recruited. Out of 1785 women, 929 were identified as part of the high-risk group. Due to missing data from 74 pregnant women within the high-risk group, the analysis was conducted in 855 women (Figure 2). The mean gestational age at the time of screening was 12.3 ± 2 weeks. The mean of haemoglobin was 121 ± 13 (68-174 g/l) and the median of ferritin 40 µg/l (4-5607 µg/l) (Table 1).

Table 1.

Haematological data and serum iron status (n=855).

| Parameter       | Value                  |
|-----------------|------------------------|
| Hb (g/l)        | 121 ± 12.7 (68-174)    |
| RBC (x10⁶/µl)   | 4.18 ± 0.45 (2.2-6.2)  |
| MCV (fl)        | 84.5 ± 7.4 (59-122.2)  |
There were 139 anaemic women (139/855; 16.3%); namely iron deficiency anaemia was identified in 75 women (75/855; 8.8%) and anaemia of other aetiology in 64 women (64/855; 7.5%) (Figure 2). There were 242 women with iron deficiency (242/855; 28.3%). The mean of haemoglobin, serum ferritin and CRP of each group are presented in Table 2.

|             |                |
|-------------|----------------|
| MCH (pg)    | 24.2 ± 3.7 (19.2-32.9) |
| HRC (%)     | 0.8 (0-58.2)    |
| RDW (%)     | 14.2 ± 1.9 (11.7-32.1) |
| Reticulocytes (%) | 18.5 ± 5.1 (7-38) |
| Ferritin (µg/l) | 40 (4-5607)     |
| CRP (mg/l)  | 4.1 (0.3-89.9)  |

Table 2.
The haematological data of the four groups (n=855).

Group 1: normal (474); group 2: ID (242); group 3: IDA (75); group 4: anaemia of other causes (64).

|                | Group 1 |        | Group 2 |        | Group 3 |        | Group 4 |        |
|----------------|---------|--------|---------|--------|---------|--------|---------|--------|
|                | Mean (SD) | Range  | Mean (SD) | Range  | Mean (SD) | Range  | Mean (SD) | Range  |
| Hb (g/l)       | 125 (8.1) | 110-155 | 124 (8.5) | 110-148 | 100 (8.1) | 75-109 | 100 (8.4) | 68-109 |
| Median         |          |        |          |        |          |        |          |        |
| CRP (mg/l)     | 3.9      | 0.3-89.9 | 4        | 0.3-141 | 5.4      | 1-27.6 | 5.1      | 1.2-19.4 |
| Ferritin (μg/l) | 62      | 30-436  | 19 (6.6) | 5-29   | 14 (6.5) | 4-27   | 73.5 (30-827) |        |

Most of the pregnant women in the screening originated from Africa (primarily Eritrea), Turkey, India and the Middle East (primarily Syria). The prevalence of haemoglobinopathies was 14.5% in the high-risk group (124/855) and 6.95% for all patients (124/1785). There were 5 women with sickle cell
anaemia, 18 with the sickle cell trait, 39 with the alpha thalassaemia trait (4 women with alpha zero thalassaemia trait and 35 with alpha plus thalassaemia trait), 42 with heterozygous beta thalassaemia, 12 with other haemoglobin variants, and 8 women with a haemoglobin variant and alpha thalassaemia (Table 3).

Table 3.

Types of haemoglobin variants.
| Haemoglobin variant               | Number of patients (%) |
|----------------------------------|------------------------|
| Beta thalassaemia                | 42 (33.9)              |
| Alpha thalassaemia trait         | 39 (31.5)              |
| - Heterozygous                   | 27                     |
| - Homozygous                     | 12                     |
| Sickle cell anaemia              | 23 (18.5)              |
| - Heterozygous                   | 18                     |
| - Homozygous                     | 5                      |
| Other haemoglobins               | 12 (9.7)               |
| - Heterozygous Delta thalassaemia| 3                      |
| - Haemoglobin E                  | 6                      |
| - Heterozygous haemoglobin E     | 5                      |
| - Homozygous haemoglobin E       | 1                      |
| - Heterozygous haemoglobin C     | 1                      |
| Compound haemoglobin | Count |
|----------------------|-------|
| - Heterozygous haemoglobin D | 2     |
| - Heterozygous sickle cell anaemia/ heterozygous alpha thalassaemia | 4     |
| - Heterozygous sickle cell anaemia/ homozygous alpha thalassaemia | 1     |
| - Heterozygous sickle cell anaemia/ homozygous alpha thalassaemia | 1     |
| - Heterozygous haemoglobin C/ homozygous alpha thalassaemia | 1     |
| - Heterozygous haemoglobin E/ heterozygous alpha thalassaemia | 1     |

(8 (6.4) total)
The mean of haemoglobin was 111 ± 14 (79-162 g/l) and the median of ferritin 54 µg/l (5-5607 µg/l). There were 48 anaemic women with a haemoglobin variant (48/104; 46.2%) and 56 were non-anaemic (56/104; 53.8%), (Figure 3). Of the identified women with a haemoglobin variant, 15 showed iron deficiency anaemia in the first trimester (15/104; 14.4%), (Figure 3). There were 33 women with a haemoglobin variant and concomitant iron deficiency found. In 71 pregnant women with a haemoglobin variant the
ferritin was ≥ 30 µg/l. In 12 women the ferritin was ≥ 150 µg/l (12/104; 11.5%),

2 women presented alpha thalassaemia, 6 beta thalassaemia and 4
homozygous sickle cell anaemia. There was a very low mean of MCV and
MCH in the group of women with alpha and beta thalassaemia (mean MCV
70 ± 7 fl [59-88] and MCH 23 ± 3 pg [16.3-31.6]). In 23 pregnant women
(23/124) a haemoglobin variant was previously diagnosed and 101 women
were diagnosed based on our screening (101/124).
Discussion

Population movements affect the distribution of inherited disorders of haemoglobin within countries, with previously isolated populations increasingly interacting and large numbers of migrants moving from rural to urban areas, the complexity of genotypes can be observed as newly introduced variants may interact with local ones to create more or less severe phenotypes (13).

The prevalence of haemoglobinopathies of 6.95% (124/1785) in total in our study group corresponds to an overall average of 8% (14). In the high-risk group of women, the prevalence of haemoglobinopathies was twice as high (124/855; 14.5%). Using the family origin questionnaire, we identified a group of pregnant women with haemoglobinopathies, which might have otherwise been overlooked. Half of the pregnant women with
haemoglobinopathies were non-anaemic and two-thirds of them had normal iron status in the first trimester. One third of the women with haemoglobinopathies showed anaemia with normal iron status in the first trimester. The majority of pregnant women in the screening originated from Africa, Turkey, the Middle East and India. Due to political changes significant more women were reported from Syria and Eritrea in the last few years.

In the UK, where there is a well-established, linked neonatal and antenatal screening programme for haemoglobinopathies, a downward trend in reported screen-positive results is discernible in some areas (8). In contrast, Germany, Italy and France have recently been accepting large numbers of refugees and have faced a dramatic increase in their patient numbers since 2014 (8). With the exception of Belgium, the UK, Cyprus, Greece, Germany and Spain, no national registry exists for haemoglobinopathies in European
countries (8). According to the Organisation for Economic Co-operation and Development, the percentage of foreign-born populations within the European Union in 2008 ranged from 4% in Finland to 37% in Luxembourg (14). Switzerland has one of the highest proportions of foreigners in its midst among all nations 24.6% in 2016 (14).

European countries with a high prevalence of haemoglobinopathies have adopted a neonatal screening programme (France, Belgium, the Netherlands and Spain), an early antenatal screening programme (Sweden, Italy), a linked neonatal and antenatal screening programme (UK), or a preconceptional, premarital screening programme (Cyprus, Greece and Turkey). Antenatal screening programmes are generally assessed by the uptake of prenatal diagnosis, optimal care management, and/or the allowance to terminate affected pregnancies.
The limitation of our study is the lack of HPLC in all women. However, conducting universal screening would not be cost effective in low-risk pregnant women. The choice of the screening method is based on cost-effectiveness, and it has been demonstrated that at a prevalence of at least 16 sickle cell traits/1,000 there is no significant cost difference between universal and targeted screening programmes. Therefore, targeted antenatal screening is recommended in Switzerland. On the other hand, it would be impossible to detect women with a sickle cell trait by using the full blood count alone for screening due to normal red cell blood parameters in these patients. Our findings will be used to further implement the screening in prenatal care in Basel and will be recommended among all pregnant women with a high-risk of haemoglobinopathies in Switzerland. Early recognition of haemoglobin variants in women enables early testing of partners and provides the
opportunity for further testing where required. Thereby, the ability to improve prenatal and neonatal care in these patients and to reduce the number of children with severe clinically relevant haemoglobin variants can be offered.
Contributors GAB is the principal investigator who designed the study, carried out the quantitative analysis and drafted the article. FG collected the data. IH reviewed and edited the manuscript. All authors have read and approved the final manuscript.

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Competing interests None declared.

Patient consent for publication Not required.

Data availability statement Data are available on reasonable request.
**Figure Legends**

**Figure 1:** The Family origin questionnaire.

**Figure 2:** Pregnant women on screening, on testing and completion.

Allocation of pregnant women with high-risk of haemoglobinopathy according to haemoglobin and serum ferritin.

**Figure 3:** Allocation of pregnant women with haemoglobin variants according to haemoglobin and serum ferritin.
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„Family origin questionnaire for screening of thalassaemia, sickle cell anaemia and other forms of haemoglobinopathy”

To our pregnant patients

Haemoglobinopathies are among the most common inherited disorders worldwide. As a result of the migration of people from countries with high prevalence of haemoglobin disorders, laboratory diagnosis is of growing importance in Switzerland. Countries C, D, E, F and G (See below; in red) have a high prevalence of haemoglobinopathies. Testing for haemoglobinopathies should be conducted in these women.

What are your family origins?

A. Swiss
B. Northern European
   Germany, France, Austria, Belgium,
   Netherlands, Scandinavia, Ireland, United Kingdom and so on
   Any other European family origins (white)
   (Please fill in)
   (Russia, Australia, North America, South Africa, Canada and so on)
C. Southern & Other European (white)
   Cyprus
   Greece, Turkey
   Italy, Portugal, Spain
   Any other Mediterranean country (Please fill in)
D. South Asian (Asian)
   India, Sri Lanka
   Pakistan, Afghanistan
   Bangladeshi
E. African or African-Caribbean (black)
   Caribbean Islands or Central America
   Africa (excluding North Africa) Eritrea, Ethiopia, Congo and so on
   Any other African or African-Caribbean family origins
   (Please fill in)
F. South East Asian (Asian)
   China
   Thailand
   Malaysia, Vietnam, Philippines and so on
   Any other Asian family origins (Please fill in)
G. Other Non-European (Other)
   North Africa, South America and so on
   Middle East (Saudi Arabia, Iran, Libya, Israel, Jordan and so on)
H. Decline to answer

Date of blood withdrawal
Figure 2.

On screening  
\( n = 1785 \)

- Low risk  
  \( n = 856 \)
- High risk  
  \( n = 929 \)

- Missing data  
  \( n = 74 \)
- Final analysis  
  \( n = 855 \)

- Anaemia  
  \( n = 139 \)
  - Iron deficiency anaemia  
    \( n = 75 \)
  - Anaemia of other reason  
    \( n = 64 \)
- Non- Anaemia  
  \( n = 716 \)
  - Iron deficiency  
    \( n = 242 \)
  - Normal  
    \( n = 474 \)
Figure 3.

Pregnant women with Haemoglobinopathy
n = 124

Uncompleted data
n = 20

On analysis
n = 104

Anaemic women
n = 48 (46.2%)

Iron deficiency anaemia
n = 15 (14.4%)

Anaemia of other reasons
n = 33 (31.7%)

Non-anaemic women
n = 56 (53.8%)

Iron deficiency
n = 18 (17.4%)

Normal
n = 38 (36.5%)
# Cohort profile: Targeted antenatal screening for haemoglobinopathies in Basel

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Cohort profile: Targeted antenatal screening for haemoglobinopathies in Basel

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Competition interests: None declared.
Abstract

Purpose: The pregnancy cohort was established to examine the prevalence and variety of haemoglobinopathies in a high-risk group of pregnant women.

Participants: The pregnancy cohort is located in the Department of Obstetrics and Antenatal Care, University Hospital of Basel. The pregnant women were recruited in the first trimester between June 2015 and May 2019. Family origin questionnaires were used to screen pregnant women for the risk of a haemoglobin variant. Based on the questionnaire, pregnant women were divided into two groups: women with a high-risk and women with a low risk of a haemoglobin variant. In women with a high-risk, red blood cell indices, iron status and chromatography were conducted.

Findings to date: 1785 pregnant women were recruited. Out of the 1785 women, 929 were identified as part of the high-risk group. Due to missing
data in 74 pregnant women with a high-risk, the final analysis was conducted in the remaining 855 women. The prevalence of haemoglobinopathies in the high-risk group was 14.5% (124/855).

**Future plans:** This cohort will be used to: 1) implement the screening in prenatal care in Basel; 2) recommend the screening among pregnant women with a high-risk of a haemoglobin variant in Switzerland; 3) improve prenatal and neonatal care in patients with a haemoglobin variant; 4) examine adverse pregnancy outcomes in women with a haemoglobin variant; 5) reduce maternal and neonatal morbidity and mortality in the future.
Strengths and limitations of this study

- For the first time, to our knowledge, a prospective study has been conducted to examine the prevalence and the variety of haemoglobinopathies among pregnant women in Switzerland.

- The limitation of our study is the lack of conducting of a high-performance liquid chromatography and molecular analysis in all women. However, conducting a universal screening would not be cost effective in low risk pregnant women.

- The prevalence of 14.5% in the high-risk group of pregnant women confirms an increasing significance of screening for haemoglobinopathies in this group of patients.
- Our findings provide new insights into the prevalence of haemoglobinopathies and have important implications in the health service within Switzerland.
Introduction

Haemoglobinopathies are among the most common inherited disorders worldwide. As recommended by the World Health Organisation (WHO), screening and genetic counselling for haemoglobin disorders should be an intrinsic part of health care in most counties (1). Two factors have recently highlighted the need for a more coordinated approach to diagnosis and management of haemoglobinopathies. Firstly, the globalisation of migration flows has increased cultural diversity, bringing to Europe populations from areas with a high prevalence of haemoglobinopathies, and secondly, there is an increasing the number of patients requiring health services (2-6).

In the publication “A Roadmap for European Haematology Research” (7), the European Haematology Association (EHA) in 2017 recommended undertaking detailed epidemiological studies in all countries, particularly in
Western Europe, as a prerequisite for the implementation of effective prevention programmes. Since then different policies for the antenatal and neonatal screening for haemoglobinopathies have been adapted in Europe, yet the data covering affected patients are not available to every country (8). There are a few countries with evidence of increasing numbers of patients; however, planning national strategies of increasing number of patients has not been considered at this time to the best of our knowledge (8). Although haemoglobinopathies have increased significantly in Switzerland in recent years, there is no routine prenatal and/or neonatal screening for haemoglobinopathies. Therefore, since 2015 we have been conducting targeted prenatal screening at the University Hospital of Basel to investigate the current prevalence of haemoglobinopathy and improve prenatal care in these patients.
Cohort description

A prospective, cross sectional study was conducted at the University Hospital of Basel, Department of Obstetrics and Antenatal Care between June 2015 and May 2019. Pregnant women were recruited in the first trimester from our outpatients’ department. Family origin questionnaires were used to screen pregnant women for the risk of haemoglobinopathies in the first trimester. The Family origin questionnaire was adopted from the National Health Screening: Sickle Cell and Thalassaemia Screening Programme in England (Figure 1). Based on the questionnaire, pregnant women were divided into two groups: women with a high-risk and women with a low risk of haemoglobinopathies.
In women with a high-risk, red blood cell indices, iron status and high-performance liquid chromatography (HPLC) were conducted. For women identified as carriers, their partner was also tested for haemoglobinopathy, irrespective of family origin. In cases where alpha thalassaemia was suspected based on haematological parameters (MCH< 27 pg regardless of iron status) (9), a molecular analysis was performed. If both were carriers of haemoglobinopathies, genetic counselling was recommended and an antenatal genetic testing via choriovillous sampling or amniocentesis was discussed with the patient.

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measures included a variety of haemoglobinopathies, the prevalence of anaemia, iron deficiency anaemia and iron deficiency.

Haematological Assessment

Screening for anaemia in pregnancy is generally recommended in Switzerland, including the red blood count and ferritin at the end of the first trimester (10). Therefore, blood samples were collected by venepuncture. All blood measurements (blood count, CRP, ferritin and HPLC) were conducted at the University Hospital of Basel, Department of Laboratory Medicine.

Haemoglobin (Hb), red blood cell count (RBC), haematocrit (HCT), mean corpuscular volume (MCV), mean corpuscular haemoglobin (MCH), hypochromic red blood cells (HRC) and red blood distribution width (RDW) were measured using a haematology analyser. The mean corpuscular
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Statistical analysis was conducted using STATA 12.0 (Stata Corporation College Station, TX). Blood indices, CRP and serum ferritin were expressed as mean ± standard deviation (s.d.) and range, or median and range.

Ethics and dissemination

The study received ethical approval from the local ethics committee in Basel (ID 2019-01065). It was registered under http://www.ClinicalTrials.gov
(NCT04029142) in July 2019. All members of the research team were aware of the guidelines for good clinical practice.

The findings of this study will be published in a peer-reviewed journal and presented at national scientific conferences to disseminate the results to academic and health professional audiences. In addition, they will be made available to the participants and to the wider public on our website at the time of publication.

Data sharing

After publication of the study individual, anonymous participant data, including variable keys, will be available from the corresponding author on request. Researchers may request data to repeat the analyses or use the data for secondary analyses (e.g. systematic review and meta-analysis).
Patient and public involvement

The patients and the public were neither involved in developing the hypothesis, the specific aims or the research question, nor were they involved in developing the plan for design or implementation of the study.
Findings to date

In brief, 1785 pregnant women were recruited. Out of 1785 women, 929 were identified as part of the high-risk group. Due to missing data from 74 pregnant women within the high-risk group, the analysis was conducted in 855 women (Figure 2). The mean gestational age at the time of screening was 12.3 ± 2 weeks. The mean of haemoglobin was 121 ± 13 (68-174 g/l) and the median of ferritin 40 µg/l (4-5607 µg/l) (Table 1).

Table 1.

Haematological data and serum iron status (n=855).

| Parameter   | Value               |
|-------------|---------------------|
| Hb (g/l)    | 121 ± 12.7 (68-174) |
| RBC (x10^6/µl) | 4.18 ± 0.45 (2.2-6.2) |
| MCV (fl)    | 84.5 ± 7.4 (59-122.2) |
|          |               |               |
|----------|---------------|---------------|
| MCH (pg) | 24.2 ± 3.7 (19.2-32.9) |               |
| HRC (%)  | 0.8 (0-58.2)  |               |
| RDW (%)  | 14.2 ± 1.9 (11.7-32.1) |               |
| Reticulocytes (%) | 18.5 ± 5.1 (7-38) |               |
| Ferritin (µg/l) | 40 (4-5607) |               |
| CRP (mg/l) | 4.1 (0.3-89.9) |               |

There were 139 anaemic women (139/855; 16.3%); namely iron deficiency anaemia was identified in 75 women (75/855; 8.8%) and anaemia of other aetiology in 64 women (64/855; 7.5%) (Figure 2). There were 242 women with iron deficiency (242/855; 28.3%). The mean of haemoglobin, serum ferritin and CRP of each group are presented in Table 2.

Table 2.
The haematological data of the four groups (n=855).

Group 1: normal (474); group 2: ID (242); group 3: IDA (75); group 4: anaemia of other causes (64).

|                | Group 1 |       | Group 2 |       | Group 3 |       | Group 4 |       |
|----------------|---------|-------|---------|-------|---------|-------|---------|-------|
|                | Mean (SD) | Range | Mean (SD) | Range | Mean (SD) | Range | Mean (SD) | Range |
| Hb (g/l)       | 125 (8.1) | 110-155 | 124 (8.5) | 110-148 | 100 (8.1) | 75-109 | 100 (8.4) | 68-109 |
| Median         |          |       | Median   |       | Median   |       | Median   |       |
|                | Median   |       | Mean (SD) |       | Mean (SD) |       | Mean (SD) |       |
| CRP (mg/l)     | 3.9      | 0.3-89.9 | 4        | 0.3-141 | 5.4     | 1-27.6 | 5.1     | 1.2-19.4 |
| Ferritin (μg/l)| 62       | 30-436  | 19 (6.6) | 5-29  | 14 (6.5) | 4-27  | 73.5    | (30-827) |

Most of the pregnant women in the screening originated from Africa (primarily Eritrea), Turkey, India and the Middle East (primarily Syria). The prevalence of haemoglobinopathies was 14.5% in the high-risk group (124/855) and 6.95% for all patients (124/1785). There were 5 women with sickle cell
anaemia, 18 with the sickle cell trait, 39 with the alpha thalassaemia (4 women with heterozygous alpha zero thalassaemia trait, 20 with heterozygous alpha plus thalassaemia, 12 with homozygous alpha plus thalassaemia), 42 with heterozygous beta thalassaemia, 12 with other haemoglobin variants, and 8 women with a haemoglobin variant and alpha thalassaemia (Table 3).

Table 3.

Types of haemoglobin variants.
| Haemoglobin variant                              | Number of patients (%) |
|------------------------------------------------|------------------------|
| Beta thalassaemia                               | 42 (33.9)              |
| Alpha thalassaemia trait                        | 39 (31.5)              |
| - Heterozygous alpha plus thalassaemia          | 23                     |
| - Homozygous alpha plus thalassaemia            | 12                     |
| - Heterozygous alpha zero thalassaemia          | 4                      |
| Sickle cell anaemia                             | 23 (18.5)              |
| - Heterozygous                                  | 18                     |
| - Homozygous                                    | 5                      |
| Other haemoglobins                              | 12 (9.7)               |
| - Heterozygous Delta thalassaemia               | 3                      |
| - Haemoglobin E                                 | 6                      |
|                      |       |
|----------------------|-------|
| Heterozygous haemoglobin E | 5     |
| Homozygous haemoglobin E   | 1     |
| Heterozygous haemoglobin C | 1     |
| Heterozygous haemoglobin D | 2     |
| **Compound haemoglobins** | **8 (6.4)** |
| Heterozygous sickle cell anaemia/ heterozygous alpha thalassaemia | 4     |
| Heterozygous sickle cell anaemia/ homozygous alpha thalassaemia | 1     |
| Homozygous sickle cell anaemia/ heterozygous alpha thalassaemia | 1     |
| Heterozygous haemoglobin C/ homozygous alpha thalassaemia | 1     |
| Heterozygous haemoglobin E/ heterozygous alpha thalassaemia | 1     |
The mean of haemoglobin was 111 ± 14 (79-162 g/l) and the median of ferritin 54 µg/l (5-5607 µg/l). There were 48 anaemic women with a haemoglobin variant (48/104; 46.2%) and 56 were non-anaemic (56/104; 53.8%), (Figure 3). Of the identified women with a haemoglobin variant, 15 showed iron deficiency anaemia in the first trimester (15/104; 14.4%), (Figure 3). There were 33 women with a haemoglobin variant and concomitant iron deficiency found. In 71 pregnant women with a haemoglobin variant the ferritin was ≥ 30 µg/l. In 12 women the ferritin was ≥ 150 µg/l (12/104; 11.5%), 2 women presented alpha thalassaemia, 6 beta thalassaemia and 4...
homozygous sickle cell anaemia. There was a very low mean of MCV and
MCH in the group of women with alpha and beta thalassaemia (mean MCV
70 ± 7 fl [59-88] and MCH 23 ± 3 pg [16.3-31.6]). In 23 pregnant women
(23/124) a haemoglobin variant was previously diagnosed and 101 women
were diagnosed based on our screening (101/124).
Discussion

Population movements affect the distribution of inherited disorders of haemoglobin within countries, with previously isolated populations increasingly interacting and large numbers of migrants moving from rural to urban areas, the complexity of genotypes can be observed as newly introduced variants may interact with local ones to create more or less severe phenotypes (13).

The prevalence of haemoglobinopathies of 6.95% (124/1785) in total in our study group corresponds to an overall average of 8% (14). In the high-risk group of women, the prevalence of haemoglobinopathies was twice as high (124/855; 14.5%). Using the family origin questionnaire, we identified a group of pregnant women with haemoglobinopathies, which might have otherwise been overlooked. Half of the pregnant women with
haemoglobinopathies were non-anaemic and two-thirds of them had normal iron status in the first trimester. One third of the women with haemoglobinopathies showed anaemia with normal iron status in the first trimester. The majority of pregnant women in the screening originated from Africa, Turkey, the Middle East and India. Due to political changes significant more women were reported from Syria and Eritrea in the last few years.

In the UK, where there is a well-established, linked neonatal and antenatal screening programme for haemoglobinopathies, a downward trend in reported screen-positive results is discernible in some areas (8). In contrast, Germany, Italy and France have recently been accepting large numbers of refugees and have faced a dramatic increase in their patient numbers since 2014 (8). With the exception of Belgium, the UK, Cyprus, Greece, Germany and Spain, no national registry exists for haemoglobinopathies in European
countries (8). According to the Organisation for Economic Co-operation and Development, the percentage of foreign-born populations within the European Union in 2008 ranged from 4% in Finland to 37% in Luxembourg (14). Switzerland has one of the highest proportions of foreigners in its midst among all nations 24.6% in 2016 (14).

European countries with a high prevalence of haemoglobinopathies have adopted a neonatal screening programme (France, Belgium, the Netherlands and Spain), an early antenatal screening programme (Sweden, Italy), a linked neonatal and antenatal screening programme (UK), or a preconceptional, premarital screening programme (Cyprus, Greece and Turkey). Antenatal screening programmes are generally assessed by the uptake of prenatal diagnosis, optimal care management, and/or the allowance to terminate affected pregnancies.
The limitation of our study is the lack of HPLC in all women. However, conducting universal screening would not be cost effective in low-risk pregnant women. The choice of the screening method is based on cost-effectiveness, and it has been demonstrated that at a prevalence of at least 16 sickle cell traits/1,000 there is no significant cost difference between universal and targeted screening programmes. Therefore, targeted antenatal screening is recommended in Switzerland. On the other hand, it would be impossible to detect women with a sickle cell trait by using the full blood count alone for screening due to normal red cell blood parameters in these patients. Our findings will be used to further implement the screening in prenatal care in Basel and will be recommended among all pregnant women with a high-risk of haemoglobinopathies in Switzerland. Early recognition of haemoglobin variants in women enables early testing of partners and provides the
opportunity for further testing where required. Thereby, the ability to improve prenatal and neonatal care in these patients and to reduce the number of children with severe clinically relevant haemoglobin variants can be offered.
Contributors GAB is the principal investigator who designed the study, carried out the quantitative analysis and drafted the article. FG collected the data. IH reviewed and edited the manuscript. All authors have read and approved the final manuscript.

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Competing interests None declared.

Patient consent for publication Not required.

Data availability statement Data are available on reasonable request.
Figure Legends

Figure 1: The Family origin questionnaire.

Figure 2: Pregnant women on screening, on testing and completion. Allocation of pregnant women with high-risk of haemoglobinopathy according to haemoglobin and serum ferritin.

Figure 3: Allocation of pregnant women with haemoglobin variants according to haemoglobin and serum ferritin.
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"Family origin questionnaire for screening of thalassaemia, sickle cell anemia and other forms of haemoglobinopathy"

To our pregnant patients

Haemoglobinopathies are among the most common inherited disorders worldwide. As a result of the migration of people from countries with high prevalence of haemoglobin disorders, laboratory diagnosis is of growing importance in Switzerland. Countries C, D, E, F and G (See below; in red) have a high prevalence of haemoglobinopathies. Testing for haemoglobinopathies should be conducted in these women.

What are your family origins?

|                          | Mother-to-be | Father-to-be |
|--------------------------|-------------|-------------|
| **A. Swiss**             |             |             |
| B. Northern European     |             |             |
| Germany, France, Austria, Belgium, Netherlands, Scandinavia, Ireland, United Kingdom and so on |             |             |
| Any other European family origins (white) (Please fill in) |             |             |
| Russia, Australia, North America, South Africa, Canada and so on |             |             |
| **South-East Europa**    |             |             |
| Kosovo, Macedonia, Serbia, Albania, Bosnia-Herzegovina, Croatia, Slovenia, Romania, Bulgaria, Hungary, Poland, Slovakia, Czech Republic |             |             |
| **C. Southern & Other European (white)** |             |             |
| Cyprus, Greece, Turkey, Italy, Portugal, Spain |             |             |
| Any other Mediterranean country (Please fill in) |             |             |
| **D. South Asian (Asian)** |             |             |
| India, Sri Lanka, Pakistan, Afghanistan, Bangladesh |             |             |
| **E. African or African-Caribbean (black)** |             |             |
| Caribbean Islands or Central America, Africa (excluding North Africa) Eritrea, Ethiopia, Congo and so on |             |             |
| Any other African or African-Caribbean family origins (Please fill in) |             |             |
| **F. South East Asian (Asian)** |             |             |
| China, Thailand, Malaysia, Vietnam, Philippines and so on |             |             |
| Any other Asian family origins (Please fill in) |             |             |
| **G. Other Non-European (Other)** |             |             |
| North Africa, South America and so on |             |             |
| Middle East (Saudi Arabia, Iran, Libya, Israel, Jordan and so on) |             |             |

H. Decline to answer

Date of blood withdrawal

Gesamtleitung/Chefarztin Frauenklinik des Universitätsspitals Basel: Prof. Dr. med. Viola Heinzelmann-Schwarz
Gynäkologie und Gyn. Onkologie: Chefarzt: Prof. Dr. med. Viola Heinzelmann-Schwarz, Chefarzt Senologie: PD Dr. med. Christian Kurzeder
Stv. Chefarzt: Dr. med. André Kind, MPH (Gyn), Leitender Arzt: Dr. med. Bernhard Felinmann-Fischer, MBA
Geburtskunde und Schwangerschaftsmedizin: Chefarzt: Prof. Dr. med. Irene Hößli, Stv. Chefarzt: Prof. Dr. med. Olav Lapaire
Endokrinologie und Reproduktionsmedizin: Chefarzt: Prof. Dr. med. Christian De Geyter
Gyn. u. Endokrinologie: Chefarzt: PD Dr. med. Sibylle Tschudin
Gyn. Sonographie und Pränataldiagnostik: Leitender Arzt PD Dr. med. Gwendolin Manegold-Brauer, Stv. Prof. Dr. med. Olav Lapaire
Poliklinik: Leitender Arzt Dr. med. André Kind, MPH

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Figure 2.

On screening  
\( n = 1785 \)

Low risk  
\( n = 856 \)

High risk  
\( n = 929 \)

Missing data  
\( n = 74 \)

Final analysis  
\( n = 855 \)

Anaemia  
\( n = 139 \)

Iron deficiency anaemia  
\( n = 75 \)

Anaemia of other reason  
\( n = 64 \)

Iron deficiency  
\( n = 242 \)

Normal  
\( n = 474 \)

Non-Amaemia  
\( n = 716 \)
Figure 3.

Pregnant women with Haemoglobinopathy
n = 124

Uncompleted data
n = 20

On analysis
n = 104

Anaemic women
n = 48 (46.2%)

Iron deficiency anaemia
n = 15 (14.4%)

Anaemia of other reasons
n = 33 (31.7%)

Non-anaemic women
n = 56 (53.8%)

Iron deficiency
n = 18 (17.4%)

Normal
n = 38 (36.5%)

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