

# Preconception Optimization of Glucose and Insulin Metabolism in Women Wanting to Conceive – High Rate of Spontaneous Conception Prior to Planned Assisted Reproduction

## Präkonzeptionelle Optimierung des Glukose- und Insulinstoffwechsels bei Kinderwunschpatientinnen – hohe Spontankonzeptionsrate vor geplanter assistierter Reproduktion

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### Schlüsselwörter

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### ABSTRACT

**Background** A hyperglycemic metabolic status with insulin resistance can have a negative effect on fertility and pregnancy outcomes. The aim of this retrospective study was to

investigate disorders of glucose and insulin metabolism in women wanting to conceive who conceived spontaneously prior to planned assisted reproduction (ART). Associated risk factors of patients in terms of live births and miscarriages were also analyzed.

**Method** Out of total study population of 589 pregnancies, the pregnancies of 129 women wishing to have children who conceived spontaneously prior to planned ART were analyzed in more detail. A 75 g OGTT (OGTT: oral glucose tolerance test) was carried out prior to conception and after determination of pregnancy, including glucose measurement and testing of insulin resistance. If anomalies or risk factors for gestational diabetes (GDM) were detected, patients received metformin therapy prior to conception (off-label use). The course and outcome of pregnancies in the defined cohort were recorded.

**Results** The rate of spontaneous conception before planned ART after treatment for disorders of glucose/insulin metabolism was 21.9% (n = 129/589). 66.7% of the 129 pregnancies resulted in a live birth, 32 patients had a miscarriage. 76.0% of patients were treated with metformin (off-label use) for polycystic ovary syndrome (PCOS), positive risk profile for GDM, or abnormal glucose/insulin metabolism prior to conception. 55.8% of the cohort developed GDM. The insulin requirements of patients with GDM differed significantly depending on their metformin intake. 24.6% of GDM patients receiving metformin treatment developed GDM requiring insulin treatment compared to 53.8% who did not receive metformin medication. The PCOS rate in the study population who had live births was significantly higher (57.0%) than in the group who had miscarriages (31.3%). There were no significant differences with regard to rate of live births and rate of miscarriages with/without metformin treatment and GDM and metformin intake.

**Conclusion** The high rate of spontaneous conceptions in the cohort of women wishing to conceive emphasizes the importance of optimizing glucose/insulin metabolism prior to conception. The high rate of GDM in a cohort of pregnant women with a history of sterility also emphasizes the importance of expanding diagnostic testing for sterility to include the inves-

tigation of glucose metabolism and testing for insulin resistance. It is possible that PCOS patients in particular could benefit from treatment with metformin prior to conception, and this could explain the high rate of live births in this patient cohort.

## ZUSAMMENFASSUNG

**Fragestellung** Eine hyperglykämische Stoffwechsellage und eine Insulinresistenz können einen negativen Einfluss auf Fertilität und Schwangerschaftsoutcome haben. Ziel dieser retrospektiven Studie war die Untersuchung der Glukose- und Insulinstoffwechselstörungen von Kinderwunschpatientinnen mit Spontankonzeption vor geplanter assistierter Reproduktion (ART). Analysiert wurden assoziierte Risikofaktoren der Patientinnen in Bezug auf Lebendgeburt oder Abort.

**Methodik** Aus einer Gesamtkohorte von 589 Schwangerschaften wurden 129 Kinderwunschpatientinnen mit Spontankonzeption vor geplanter ART genauer analysiert. Präkonzeptionell sowie nach Feststellung einer Schwangerschaft erfolgte ein 75-g-oGTT (oGTT: oraler Glukosetoleranztest) mit Glukosemessung und Insulinresistenztestung. Bei Auffälligkeiten oder Risikofaktoren für Gestationsdiabetes (GDM) erfolgte eine präkonzeptionelle Metformintherapie (Off-Label-Use). Der Schwangerschaftsverlauf sowie das Schwangerschaftsoutcome der definierten Kohorte wurden erhoben.

**Ergebnis** Die Spontankonzeptionsrate vor geplanter ART nach therapeutischer Intervention bei Auffälligkeiten im Glu-

kose-/Insulinstoffwechsel lag bei 21,9% (n = 129/589). In 66,7% der 129 Schwangerschaften kam es zur Geburt, 32 Patientinnen erlitten einen Abort. 76,0% wurden aufgrund eines polyzystischen Ovarsyndroms (PCOS), eines positiven GDM-Risikoprofils oder präkonzeptionell auffälligen Glukose-/Insulinstoffwechsels mit Metformin (Off-Label-Use) behandelt. 55,8% der Kohorte entwickelten einen GDM. Einen signifikanten Unterschied zeigten GDM-Patientinnen hinsichtlich des Insulinbedarfs in Abhängigkeit zur Metformineinnahme. 24,6% der GDM-Patientinnen unter Metformintherapie entwickelten einen insulinbehandelten GDM, ohne Metforminmedikation 53,8%. Die PCOS-Rate in der Studienpopulation mit Lebendgeburt war signifikant höher (57,0%) als bei den Abortpatientinnen (31,3%). Es zeigte sich kein signifikanter Unterschied hinsichtlich Geburt- und Abortrate mit/ohne Metformin sowie GDM und Metformineinnahme.

**Schlussfolgerung** Die hohe Spontankonzeptionsrate der Kinderwunschkohorte unterstreicht die Bedeutung der präkonzeptionellen Glukose-/Insulinstoffwechsellage für die Fruchtbarkeit. Zudem unterstreicht die hohe Rate an GDM bei Schwangeren mit Sterilitätsanamnese die Wichtigkeit, die Sterilitätsdiagnostik auf die Untersuchung des Glukosestoffwechsels und Testung auf Insulinresistenz zu erweitern. Möglicherweise profitierten zudem gerade PCOS-Patientinnen von der präkonzeptionellen Metforminmedikation, was die hohe Lebendgeburtenrate in dieser Patientinnengruppe erklärt.

## Introduction

Sterility affects between 8 and 12% of all couples of reproductive age [1]. In addition to causes of acquired sterility such as tubal defects due to sexually transmitted disease, the main causes for the rise in female sterility rates recorded in recent years are overweight, obesity, polycystic ovary syndrome (PCOS) and increasing maternal age [2, 3].

It is known in assisted reproduction medicine that overweight can result in poorer oocyte quality, lower embryo development rates and lower chances of implantation [4]. The prevalence of obesity and type 2 diabetes mellitus (DM) has continually increased in recent years, particularly in women in the reproductive age group. Just under 25% of all women in Germany are obese and more than 50% are overweight [5]. Obesity, overweight, high maternal age and PCOS are risk factors for sterility but also for developing gestational diabetes [6]. Women with a history of sterility should be investigated for risk factors for gestational diabetes; if they have weight problems, PCOS, and higher maternal age, metabolic tests should be done prior to conception and treatment initiated where appropriate.

This retrospective study analyzed a patient cohort of 129 women wishing to have children who conceived spontaneously before having planned assisted reproduction (ART) out of a total patient cohort of 589 pregnancies. The aim of this retrospective evaluation was to analyze this defined cohort of patients (n = 129) who conceived spontaneously before ART and to define its risk profile

with regard to age, body mass index, history of recurrent miscarriage, glucose and insulin metabolism, medication, complications of pregnancy, birth and GDM. The secondary aim of the study was to look for associated influences with regard to live births or miscarriages in the defined cohort. The risk profiles (in terms of glucose and insulin metabolism) of patients who conceived spontaneously and had live births were compared to those of women who had a miscarriage in early pregnancy.

## Patients and Method

This retrospective study analyzed a cohort of 129 women wishing to become pregnant who attended a center for reproductive medicine between 1 July 2011 and 31 December 2013 for assisted reproductive treatment and who conceived before undergoing the planned ART treatment (► **Fig. 1**). Out of a total of 589 pregnancies which occurred in the above-mentioned period, 460 pregnancies were the result of ART and 129 pregnancies were conceived spontaneously. Patients with positive  $\beta$ -hCG values ( $\geq 5$  IU/l) in the above-mentioned period were included in the study.

Prior to conception, the patients underwent extensive diagnostic testing to determine causes of sterility and had a 75 g OGTT (OGTT: oral glucose tolerance test) with concurrent measurement of insulin and glucose (point in time – TP fasting/60/120 min). Impaired glucose metabolism prior to conception was diagnosed if fasting glucose values were abnormal (100–125 mg/

dl, i.e. 5.6–6.9 mmol/l) or glucose tolerance was impaired (2 h plasma glucose within OGTT range of 140–199 mg/dl, i.e. 7.8–11.0 mmol/l). In this study, disorders of glucose metabolism prior to conception were additionally defined as glucose values which exceeded threshold values for gestational diabetes (fasting glucose value  $\geq 92$  mg/dl, 1-hour glucose value  $\geq 180$  mg/dl or 2-hour glucose value  $\geq 153$  mg/dl) [7]. The following empirical threshold values for insulin metabolism were defined for the study: fasting  $\geq 10$  mU/l, 1-hour value  $\geq 50$  mU/l, 2-hour value  $\geq 25$  mU/l (► **Table 1**). Women who presented with abnormal glucose/insulin values prior to conception or had a history of risk factors for developing GDM were started on metformin treatment (off-label use). All women who became pregnant through spontaneous conception identified by positive  $\beta$ -hCG test results immediately had a 2nd diagnostic 75 g OGTT to test for early-onset gestational diabetes. If glucose values in early pregnancy were unremarkable, the OGTT was repeated between GW (week of gestation) 24 + 0 and GW 27 + 6, in accordance with the relevant guidelines [7]. The course of pregnancy and pregnancy outcome (live birth/miscarriage) were recorded for all women.

## Statistical Analysis

The SPSS Statistics software package, version 22.0 (IBM Corp., New York, NY, USA) was used for data analysis. The level of significance was defined as  $p < 0.05$ . Linear regression analysis and coefficient of determination  $R^2$  were used to evaluate relationships between variables, with  $R^2 = 0$  indicating no relationship and  $R^2 = 1$  indicating that the entire variance of the dependent variable was explained by the independent variable.

## Results

### Demographic data

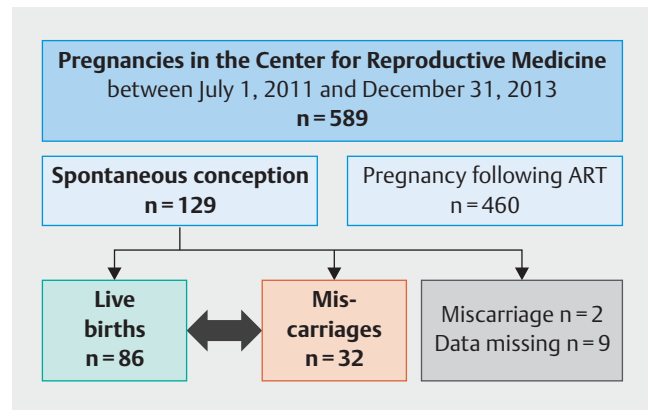
The rate of spontaneous conception in the described study population ( $n = 589$ ) after diagnostic testing for sterility and prior treatment of abnormal glucose/insulin metabolic levels (nutrition counseling, physical exercise, metformin) was 21.9% ( $n = 129$ ). The most important demographic data of the women who conceived spontaneously are summarized in ► **Table 2**.

The BMI distribution of the study population according to the criteria of the WHO is shown in ► **Fig. 2**; more than 70.0% of the women were of normal weight.

86 of the 129 patients (66.7%) who conceived spontaneously gave birth to a healthy infant; 32 (24.8%) women had a miscarriage. 33.3% ( $n = 29$ ) of the live births were delivered by C-section, the rate of premature deliveries was 10.0%. The median birth weight was 3250 g. In the overall evaluation, there was no statistically significant difference in birth weight between infants born to GDM mothers and those born to non-GDM mothers. Analysis of coagulation disorders, thyroid disease and previous ART showed no significant effect on rates of miscarriages and live births.

### Metformin

98 women (76.0%) were treated with metformin prior to conception because they had risk factors which predisposed them to de-



► **Fig. 1** Flow chart of the study design.

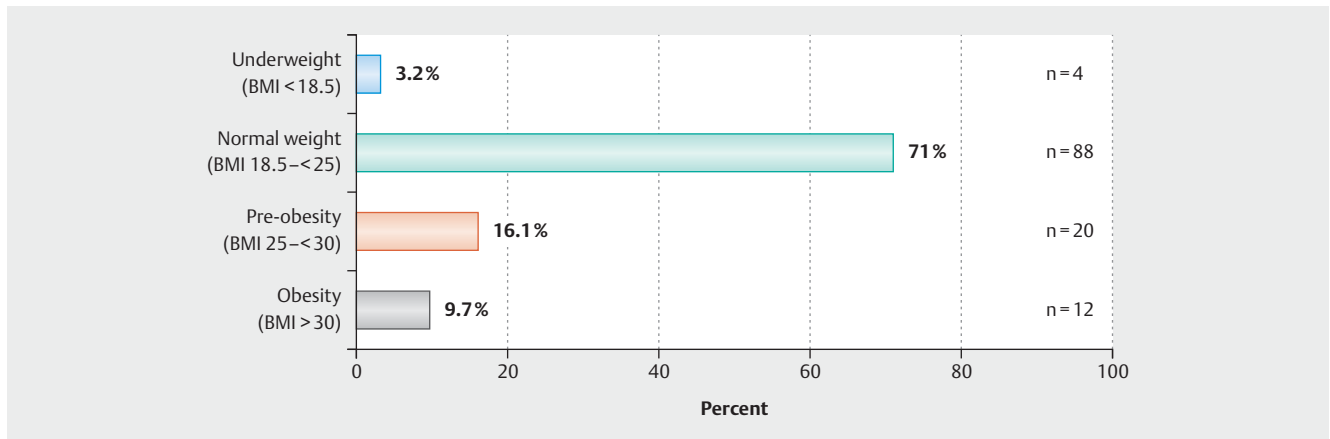
► **Table 1** Diagnostic threshold values in venous plasma for a diagnosis of gestational diabetes based on the IADPSG consensus recommendations (2010) and empirical insulin threshold values for a diagnosis of disorder of insulin metabolism.

Time of measurement	Glucose value (mg/dl)	Glucose value (mmol/l)	Insulin value (mU/l)
Fasting	92	5.1	10
After 1 hour	180	10.0	50
After 2 hours	153	8.5	25

► **Table 2** Demographic data and medical history of patients who conceived spontaneously after attending a center for reproductive medicine. Data are presented as means or percentages (absolute figures).

	Study population (n = 129)
Age (years)	32.74
Body mass index (BMI)	23.51
Primary sterility	46.5% (60)
Secondary sterility	53.5% (69)
Nullipara	74.4% (96)
Multipara	25.7% (33)
Recurrent miscarriage	43.3% (55)
PCOS	51.2% (66)
Coagulation disorder	22.5% (29)

velop GDM or PCOS or had abnormal glucose/insulin values. After starting with a low dose, the daily metformin intake of 74.5% ( $n = 73$ ) of patients was 1500 mg/day. 19.4% ( $n = 20$ ) of patients took 2000 mg of metformin per day. 5.1% ( $n = 5$ ) of patients had individually adjusted doses of metformin because of fluctuating side effects.



► **Fig. 2** BMI distribution according to the criteria of the WHO.

Intake of metformin had no significant effect on miscarriage rates (75.0% metformin intake) or rates of live births (76.7% metformin intake) ( $p = 0.843$ ).

### Disorders of glucose metabolism and gestational diabetes

The analyzed 129 spontaneous pregnancies, broken down into gestational diabetes with a further subdivision into pathological OGTT, treatment, and pregnancy outcomes, are shown as a flow chart in ► **Fig. 3**.

The baseline OGTT ( $n = 95$ ) prior to conception of 19.8% ( $n = 8$ ) of women showed glucose values which were higher than the diagnostic threshold values for gestational diabetes. Overall, 55.8% ( $n = 72$ ) of the 129 patients developed GDM. In 84.6% of patients, GDM was already diagnosed in the 1st trimester of pregnancy. Of the women who were diagnosed with a disorder of glucose metabolism even prior to conception, 77.8% ( $n = 14$ ) went on to develop GDM. Of the patients who had unremarkable values prior to conception, 62.3% ( $n = 48$ ) developed GDM during the course of pregnancy ( $p = 0.215$ ). There was a significant difference ( $p < 0.05$ ) in the group of GDM patients with regard to developing insulin dependence, and this difference depended on their metformin intake. 24.6% ( $n = 14$ ) of GDM patients receiving metformin developed insulin-requiring GDM, while the percentage of women with GDM requiring insulin who did not receive metformin treatment was 53.8% ( $n = 7$ ).

Overall, 31.1% ( $n = 22$ ) of women diagnosed with GDM had a positive familial risk profile. 63.3% ( $n = 50$ ) of women who had a live birth developed GDM during pregnancy. Of the women who had a miscarriage, only 46.9% ( $n = 15$ ) of women were diagnosed with GDM. Moreover, in our study population, a history of miscarriage and a maternal age of  $>/< 35$  years were not significant risk factors for developing GDM ( $p > 0.05$ ).

### Polycystic ovary syndrome

The PCOS rate for the total study population was 51.6% ( $n = 66$ ). The PCOS rate for the cohort of women who had live births was significantly higher compared to that of the cohort of women

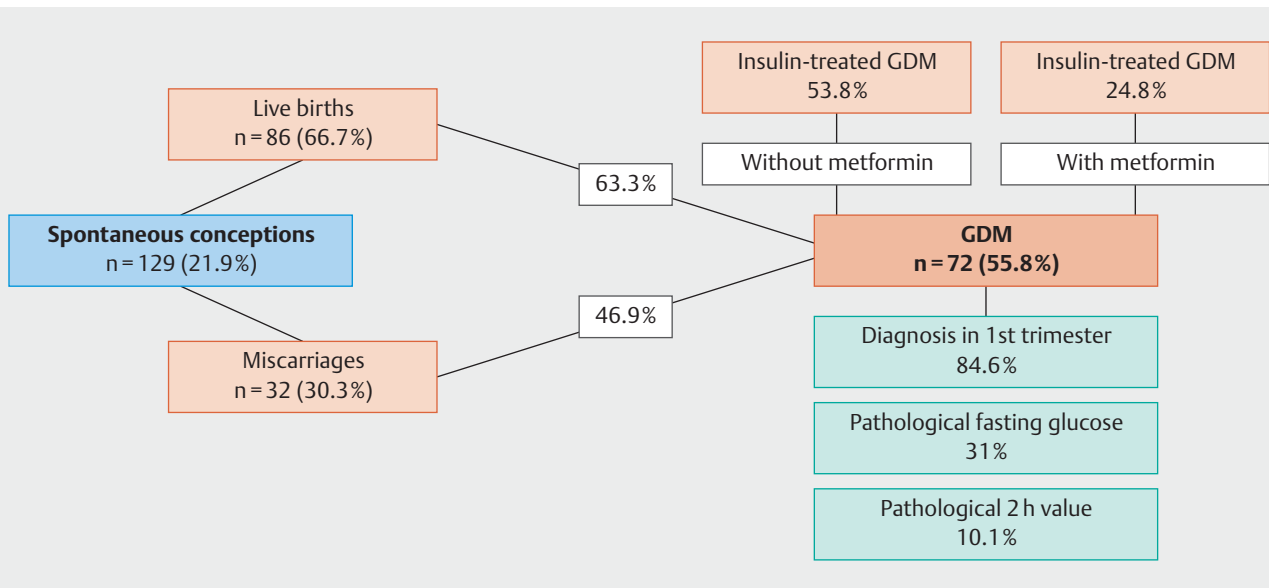
who had miscarriages (57.0%,  $n = 49$  vs. 31.3%,  $n = 10$ ;  $p < 0.05$ ). 27.3% of PCOS patients who were not treated with metformin ( $n = 13$ ) had a miscarriage, while only 14.6% of women ( $n = 53$ ) who received metformin had a miscarriage ( $p = 0.312$ ). 54.2% ( $n = 39$ ) of patients with GDM had concomitant PCOS ( $p = 0.375$ ). There was no statistical difference ( $p = 0.53$ ) between the GDM rate in the group of PCOS patients who received metformin (60.4%) and GDM rate of those who did not (53.8%).

### Insulin resistance

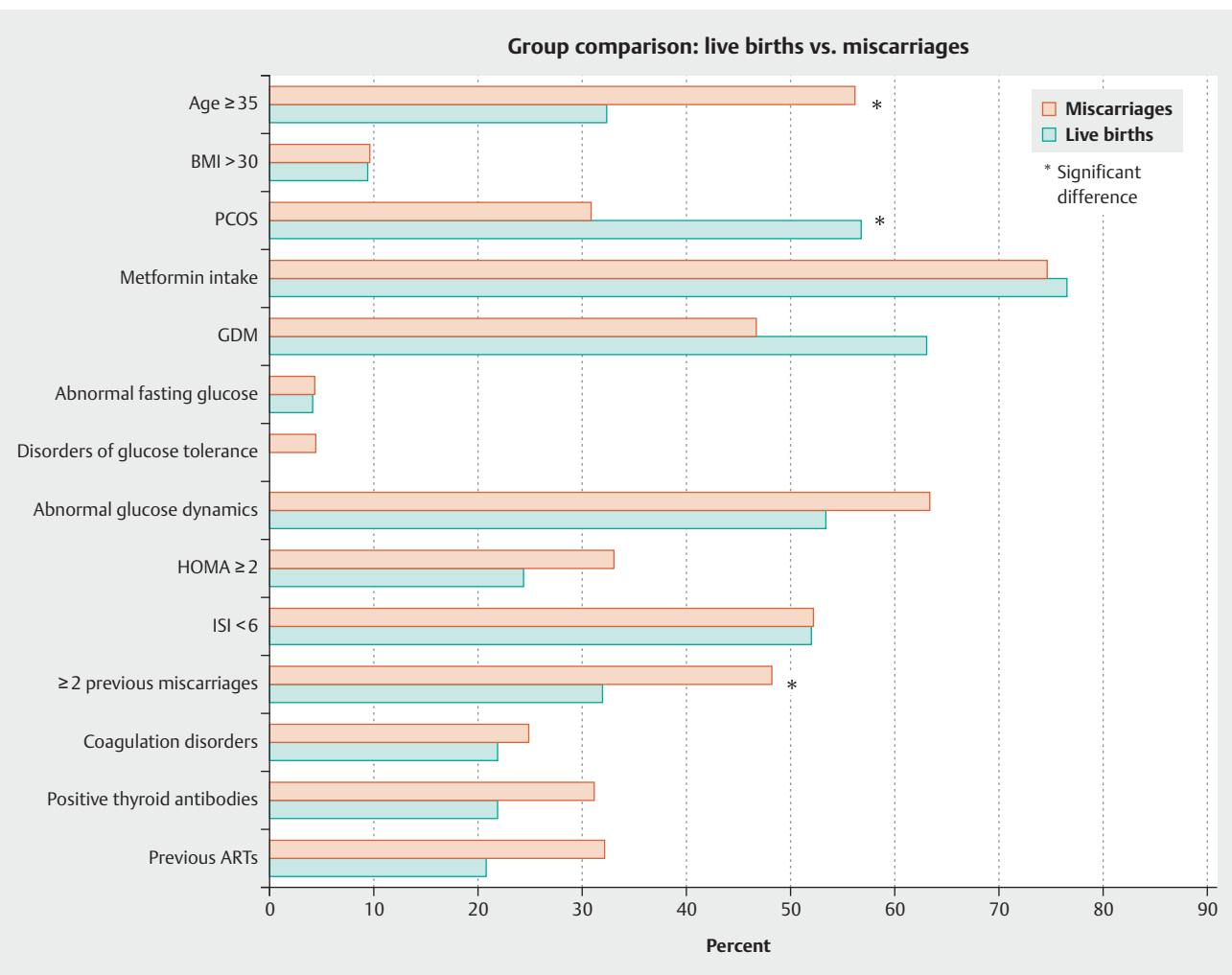
The empirically determined threshold insulin values (fasting value  $\geq 10$  mU/l, 1-hour value  $\geq 50$  mU/l, 2-hour value  $\geq 25$  mU/l) were exceeded in 87.8% of patients whose insulin levels were measured prior to conception. The insulin sensitivity index (ISI) showed abnormal insulin values for 52.1% of patients and the HOMA index ( $\geq 2$ ) showed abnormal values for 26.0% of patients. In 56.0% of cases, women had PCOS in addition to insulin resistance. Of the patients who had insulin resistance even before they became pregnant, 63.7% developed GDM. A preconception diagnosis of insulin resistance had no significant impact on whether the patient developed GDM ( $p = 0.844$ ). As regards the birth rate, rate of miscarriages and development of GDM, there were no significant differences between women who had abnormal and those who had normal ISI or HOMA index values ( $p = 0.987$ ). A significant correlation ( $p = 0.001$ ) with a large effect size ( $R^2 = 0.11$ ) was found between the HOMA index and patients' BMI: the higher the BMI, the higher the HOMA index.

### Age and BMI

When group comparisons were done to compare the group of women with miscarriages with the group of women who gave birth to a child, there was a significant difference ( $p = 0.019$ ) with regard to patient age (► **Fig. 4**). Of the group aged  $< 35$  years, 19.4% had a miscarriage; in contrast, the rate of miscarriages in the group aged  $> 35$  years was significantly higher at 39.1% ( $p = 0.032$ ). In the group of patients with a history of miscarriage ( $\geq 2$  miscarriages), the rate of miscarriages was significantly higher ( $p = 0.009$ ) (► **Fig. 4**).



► **Fig. 3** Schematic flow chart of the analyzed 129 spontaneous pregnancies categorized according to gestational diabetes and subdivided into pathologically abnormal OGTT results, treatment and pregnancy outcome.



► **Fig. 4** Overview of the risk profile of the cohort who had miscarriages compared to the cohort who had live births.

## Discussion

The most important results of this study are:

1. the high rate of spontaneous conceptions (21.9%) among women wishing to have children, which could be due to therapeutic optimization of disorders of glucose and insulin metabolism prior to conception;
2. the evidence that 70.0% of the participants in the study were of normal weight, which qualifies the increased risk of disorders of glucose and insulin metabolism due to obesity;
3. that 87.8% of the women who wanted to have children (high-risk cohort) had anomalous insulin levels even before conception; 76.0% of the total study population received treatment with metformin prior to conception;
4. that the GDM rate in the total cohort (high-risk cohort: women wanting to have children) was 55.8%; in 84.6% of cases GDM was already diagnosed in the 1st trimester of pregnancy;
5. that significantly fewer GDM patients developed insulin-dependent GDM if they received metformin.

### Overweight and obesity

The prevalence of obesity both globally and in Germany has continually increased in recent years. The “Study on the Health of Adults in Germany” found that, in the period between 2008 and 2011, 53.0% of women were pre-obese and 23.9% were obese [5]. In our study, 16.1% of patients were pre-obese and 9.7% were obese. The low prevalence of pre-obesity and obesity in our study population could be due to the relatively young patient age of the population and the usually higher social status of the women wishing to become pregnant, which is also associated with a lower prevalence of obesity in women [10]. The low obesity rate in our cohort qualifies the obesity-linked increased risk of disorders of glucose and insulin metabolism.

### Insulin resistance and metformin

As regards insulin metabolism, there was a very high prevalence of insulin resistance in this study population (HOMA index: 26.0% abnormal values; ISI: 52.1% abnormal values; empirical insulin threshold values: 87.8% abnormal values). It should be noted that the HOMA index and the ISI are models which allow insulin resistance to be measured and compared, but the significance of data obtained in this context remains limited [11]. In our patient population, insulin resistance was not found to have a static association with developing GDM, with the rate of live births or with the rate of miscarriages. 76.0% of the study participants received treatment with metformin prior to conceiving. Recent studies have shown that metformin can also be used effectively and safely during pregnancy; some authors already recommend its use for the treatment and prevention of gestational diabetes [12–14]. Current studies showed no significant differences with regard to neonatal weight, gestational age, state of health, perinatal mortality and rate of preterm delivery between insulin and metformin used to treat GDM; however, rates of neonatal hypoglycemia in newborns were reduced in the GDM group treated with metformin [12, 15, 16]. Data from other studies have shown that metformin can even reduce the need for insulin in patients with GDM [17]. We were able to confirm this finding in our study. Of the

GDM patients treated with metformin, significantly fewer patients ( $p = 0.038$ ) developed insulin-dependent GDM compared to the women who did not receive metformin. There was no significant difference in the overall rate of GDM between patients who had previously received metformin and those who did not. In the current GDM guideline, metformin is listed as an “off-label-use” drug option, also in combination with insulin, to treat GDM.

### GDM

The GDM prevalence of 55.8% in this study is more than 4 times higher than in the normal population [9]. This would indicate that disorders of glucose and insulin metabolism may play an important role in the fertility problems of women of normal weight wishing to have children. In our study, GDM was diagnosed in 87.8% of cases already in early pregnancy as “early GDM” or “early-onset GDM”. As many of the OGTTs carried out in early pregnancy were done during ongoing treatment with metformin, it can be assumed that the rate of early GDM was even higher. The data show that in a high-risk population with demonstrable risk factors for GDM, it is important not to wait with screening for GDM until the 24th week of gestation. Early diagnostic testing based on fasting glucose values carried out as part of 75 g OGTT and measurement of HBA<sub>1c</sub> could help prevent implantation failure and metabolic problems.

### PCOS

PCOS was diagnosed in 51.2% of analyzed patients. The GDM rate of PCOS patients was not significantly higher (59.1% vs. 52.4%;  $p = 0.375$ ). In the group of women who conceived spontaneously in our study population, the percentage of women with PCOS who had live births was significantly higher than the percentage of comparable PCOS patients who had miscarriages. It is known from the literature that PCOS patients in particular benefit from metformin treatment [18]. The administration of metformin to optimize insulin and glucose values prior to conception and at the time of implantation may help PCOS populations to conceive spontaneously and maintain a subsequent pregnancy.

### Age

The risk of sterility and miscarriage rises with increasing the age, as does the risk of developing GDM [19]. Because of a lack of awareness about the impact of age on fertility [21], it would be best if the question of wanting to have children and the effect of older age is addressed on an outpatient basis. The average age of patients in our study was 33 years. 38.9% ( $n = 50$ ) of patients were more than 35 years of age. In 2014, 16.7% of mothers in the general population were older than 35 years at delivery [20]. By comparison, the rate of women aged more than 35 years in our study population was 38.8% and thus significantly higher, which was clearly because the study cohort specifically consisted of women wanting to have children. Similarly, the comparison between two groups in our study population (miscarriage vs. live birth) showed a significant difference with respect to patient age. Overall, the rate of miscarriages in the group of women under the age of 35 years was 18.4%, but the rate for women aged more than 35 years was 36.7%.

## Birth, birth weight and mode of delivery

The C-section rate is higher for women with GDM than for the general population [22]. In our study, the C-section rate was 33.3% and thus was approximately the same as the average C-section rate in Germany reported for 2014 (32.9%) [20]. The fact that the C-section rate in our study population was not higher than average, despite the high number of GDM patients, may also be a consequence of adjusting patients' metabolic factors, which largely prevented macrosomia. In addition to increasing the rate of C-sections, GDM also increases the risk of premature rupture of membranes, premature labor and, consequently, the rate of preterm births (5 times higher compared to the general population) [23]. Optimal glycemic control significantly reduces the risk of preterm birth [24]. In our study, 90.0% of births were at term, 8.3% were preterm births (moderate to late preterm) and 1.7% of neonates were born between the 28th and the 31st week of gestation (very preterm). The rate of preterm births for the GDM cohort was 7.0% and therefore not significantly higher than that of the comparison group without GDM. It is important to note that the number of evaluated births may be too low to be statistically relevant (missing data  $n = 23$ ). The children of GDM patients have higher rates of macrosomia and are more likely to be "large for gestational age" [23]. A secondary but important risk of GDM with far-reaching consequences is intrauterine undernutrition, characterized by the symptom "small for gestational age" (SGA). Studies have shown that adults born with a lower birth weight were more likely to have disorders of glucose tolerance, insulin resistance and type 2 diabetes. Similarly, children with a low birth weight have a significantly higher cardiovascular risk and a higher risk of developing obesity, PCOS, and insulin resistance [25]. Intrauterine conditions and the epigenetic effects on children can increase the risk factors of the next generation for fertility disorders and abnormal glucose and insulin levels [26].

The Institute for Applied Quality Improvement and Research in Healthcare reported that in 2014 91.5% of children were born with a normal birth weight while 1.2% of children were born with a birth weight of more than 4500 g [20]. The median birth weight of the children in our study was 3250 g; there was no difference between the children of GDM patients and those of non-GDM patients ( $p = 0.878$ ).

## Limitations of the study

The high rate of conception of more than 20% in our study is attributed to treating existing disorders of glucose metabolism prior to conception. The study is limited by the lack of a control group and the retrospective analysis of data. Moreover, other factors influencing sterility in the total study population were not included in the analysis. Prospective case control studies on the optimization of glucose/insulin metabolism and its impact on fertility are required to confirm the data presented here.

## Conclusion

The results of the study support the hypothesis that successful metabolic optimization prior to conception may result in higher rates of spontaneous conception before starting ART. In addition, the high GDM rate among women with a history of sterility em-

phasized the importance of evaluating glucose metabolism, including testing for insulin resistance, as disorders of glucose metabolism may be a crucial factor affecting sterility in infertile women. Evaluation of glucose metabolism is necessary to optimize the ovarian micro milieu for oocyte maturation and improve nidation conditions for the embryo. A hyperglycemic metabolic state and insulin resistance may contribute to preventing pregnancy or impair placental development by inhibiting trophoblast proliferation and thus adversely affect the course of pregnancy [8]. Such early disorders of placentation can lead to miscarriage in early pregnancy; moreover, inadequate placentation can also lead to complications of pregnancy such as preeclampsia [28, 29].

GDM has far-reaching consequences for mother and child. Preventive strategies are necessary to combat further increases in impaired glucose metabolisms [27]. Impaired maternal glucose metabolism can lead to negative fetal programming from DNA methylation and histon modifications, with far-reaching and long-term consequences for the child. It is known that children born to mothers with GDM have a higher risk of obesity, hyperlipidemia, arterial hypertension, PCOS and developing diabetes mellitus in early adulthood [30, 31]. A close cooperation between physicians of reproductive medicine, gynecologists and diabetologists/endocrinologists is necessary and useful for systematic prevention, early recognition and early treatment of GDM. Such close cooperation could be the first step of preventive measures with positive epigenetic effects on glucose metabolism; early measures could thus help to avoid negative consequences for pregnant women and future generations.

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## Conflict of Interest

The authors declare that they have no conflict of interest.

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