Clinical Rheumatology (2023) 42:2445–2452
https://doi.org/10.1007/s10067-023-06650-4

ORIGINAL ARTICLE

Silicone breast implants may contribute to early-onset fetal growth restriction

Silvia Hoirisch-Clapauch[1]

Received: 27 April 2023 / Revised: 20 May 2023 / Accepted: 25 May 2023 / Published online: 5 June 2023

Abstract

Introduction There are many studies showing that silicone breast implants may affect lactation, but few analyzed whether these implants affect placentation. We observed that many mothers with growth-restricted pregnancies had inflammatory conditions, such as silicone breast implants or giardiasis.

Methods This single-center cohort study assessed the prevalence of inflammatory conditions in normotensive growth-restricted singleton pregnancies. Next, we stratified the patients according to the presence or absence of silicone breast implants, to determine whether these implants influence fetal growth restriction onset or severity.

Results Twelve (32%) of the 38 participants underwent cosmetic breast augmentation 4–18 years before pregnancy. Half of the patients with and 38% without silicone breast implants had giardiasis. Half of the mothers with and 35% without silicone breast implants had autoantibodies. Silicone breast implants were associated with a 70% increased risk of fetal growth restriction before 32 weeks' gestation (95% confidence interval [CI], 1.2–2.5). Fetal growth restriction was diagnosed significantly earlier in mothers with than in those without silicone breast implants, respectively at 27 (95% CI, 25–30) and 30 weeks' gestation (95% CI, 29–32). Silicone breast implants also tripled the risk of fetuses being below the third percentile, but the difference was not significant.

Conclusion Our results suggest that the association of inflammatory conditions, such as silicone breast implants, giardiasis, and autoantibodies may contribute to placental insufficiency. Silicone breast implants older than four years increased the risk of early-onset fetal growth restriction. Studies with large samples are needed to validate our findings and define whether silicone-related fetal growth restriction should be included in autoimmune/inflammatory syndrome induced by adjuvants (ASIA) criteria.

Key Points

- *Fetal growth restriction (FGR), responsible for 30% of stillbirths, is the most common cause of prematurity and intrapartum asphyxia.*
- *In this study, including 38 mothers with normotensive FGR, all participants had 2–4 inflammatory conditions, such as giardiasis, sinusitis, candidiasis, dysbiosis, extreme fear or autoantibodies.*
- *Silicone breast implants were associated with a 70% increased risk of fetal growth restriction before 32 weeks' gestation.*
- *FGR was diagnosed at 27 weeks' gestation (95% CI, 25–30) in mothers with and at 30 weeks' gestation (95% CI, 29–32) in mothers without silicone breast implants.*

Keywords ASIA syndrome · Fetal growth restriction · Giardiasis · Inflammation · Silicone

Introduction

Fetal growth restriction (FGR), defined as an estimated fetal weight or fetal abdominal circumference below the 10th percentile for gestational age [1], affects 5–10% of pregnancies [2]. By convention, FGR cases related to placental insufficiency are named FGR, while non-placental cases are referred to as small-for-gestational age fetuses [3]. The distinction between FGR and small-for-gestational

✉ Silvia Hoirisch-Clapauch
sclapauch@gmail.com

[1] Hospital Federal dos Servidores do Estado, Atlantica 434 1101, Rio de Janeiro, Brazil

age fetuses is relevant, as placental insufficiency reduces the delivery of oxygen and nutrients to the fetus [3]. FGR is responsible for 30% of stillbirths and for most cases of prematurity and intrapartum asphyxia [2], being associated with an increased risk of subtle to major neurodevelopmental disabilities [4].

Maternal factors contributing to FGR include preeclampsia and other hypertensive disorders, malnutrition, active or passive cigarette smoking, illicit drug or alcohol abuse, chronic hypoxia, severe renal diseases, increased homocysteine levels [2], hyperprolactinemia [5], and prolonged steroid use [6], but in most cases, the mechanisms underlying placental insufficiency remain unclear. Contrary to expectations, inherited thrombophilias do not increase the risk of FGR [7, 8], but cytokines, antiphospholipid antibodies, and autoimmune disorders do [9–14].

Recently, we observed that many mothers with growth-restricted fetuses had silicone breast implants (SBI). It is estimated that over 1,600,000 women worldwide underwent breast augmentation in 2020 [15]. Silicone molecules can leak, even when the capsule is intact, boosting the immune response through active immunostimulation, by providing T-cell help for antibody response, or by acting as a matrix for antigens [16].

Evidence for the immunogenicity of silicone comes from studies assessing the prevalence of antinuclear antibodies in patients with silicone implants [17]. The percentage of patients with autoantibodies varies from 5 to 36%, which can be explained by the composition and volume of the implants and the interval between implantation and antibody assessment. Other conditions that may influence immunogenicity include prior documented autoimmune reaction to other adjuvants, as in some vaccines, established autoimmune diseases, a history of allergy or atopy, genetic predisposition, and triggers [18], such as infectious disorders.

In contrast to the large cohort studies showing a negative relationship between breast implants and lactation [19], there are few reports in the literature analyzing whether SBI influence pregnancy outcomes. One of these, including 3,133 pregnancies among patients receiving silicone implants, showed that the rate of stillbirths was more than four times higher than that of the general population [20]. To our knowledge, no studies have investigated the impact of autoimmune/inflammatory syndrome induced by adjuvants (ASIA) on FGR.

Another condition highly prevalent among our patients with growth-restricted pregnancies was lactose intolerance, which is commonly seen in subjects with giardiasis. A meta-analysis of 114 studies with 98,342 pregnant women estimated that 8% of them had giardiasis [21]. *Giardia lamblia* causes duodenal inflammation that increases mucosal permeability, allowing the entry of noxious antigens into the bloodstream [22]. Mucosal damage leads to lactose malabsorption and lactose favors the proliferation of pathogenic bacteria in the small intestine and colon, amplifying inflammation. Preliminary results indicate that maternal gut dysbiosis is a risk factor for FGR [23].

Since both SBI and giardiasis may cause inflammation, we decided to assess the prevalence of inflammatory conditions in normotensive women with FGR. We then stratified the patients according to the presence (FGR+SBI) or absence of silicone breast implants (FGR–SBI) to determine whether SBI influence the onset and severity of FGR.

Methods

This observational study was approved by the local ethics committee as #19–04.111 and conducted in the department of Vascular Medicine of a Brazilian maternity hospital from February 2022 to January 2023. Pregnant women seen at our maternity hospital are routinely referred to the Vascular Medicine department by their obstetricians when abnormal placentation is suspected, which means that all enrolled participants had been pre-selected.

Inclusion criteria were normotensive mothers with growth-restricted fetuses. Exclusion criteria were fetal conditions contributing to FGR, such as gene and chromosomal mutations or intrauterine infections, multiple pregnancies, placental abruption, diabetes mellitus, renal insufficiency, malnutrition, active or passive cigarette smoking, illicit drug or alcohol abuse, chronic hypoxia, chronic steroid use or lack of follow-up until delivery.

Fetal weight percentiles were calculated using the Hadlock formula. Severe FGR was defined as estimated fetal weight below the 3rd percentile for gestational age. FGR was classified as early onset, when diagnosed before 32 weeks' gestation and late onset, when diagnosed at or after 32 weeks' gestation [24].

Medical and obstetric history, medications used, lifestyle habits, and ultrasound data were retrieved from the files. Excessive weight gain (e.g. > 1.5 kg per 4 weeks during the first half of pregnancy) was used as a surrogate of a high-carbohydrate diet. A sedentary status was defined as < 40 min per day of physical activity, including household chores.

Categorical variables included inflammatory conditions, such as injections of dermal fillers or botulinum toxin during pregnancy, and recent or current infections. Fear (characterized by increased levels of cytokines [25]) within the month prior to the diagnosis of FGR was classified as none, mild, moderate, severe or extreme. All patients complaining of lactose intolerance were screened for giardiasis with stool polymerase chain reaction (PCR). Urinary indoxyl sulfate levels (indican) were used to discriminate individuals with gut dysbiosis.

Prolactin levels, assessed during the first trimester, were retrieved from the files. Antinuclear, anti-thyroid peroxidase,

anti-thyroglobulin, anticardiolipin and anti-beta2 glycoprotein 1 antibodies, lupus anticoagulant, homocysteine, and vitamin D levels were analyzed at the time of FGR diagnosis. Patients who had not been screened for thrombophilia before pregnancy or in the first trimester, were tested at the time of FGR diagnosis, except for protein S levels, assessed after the puerperium.

Descriptive statistics were calculated with Excel (Microsoft Office 365) and R-4.2.3 for Windows. Assuming a rate of 3 FGR+SBI: 1 FGR–SBI mothers with severe growth restricted pregnancies, the sample was calculated as 76 patients, with 80% power and 5% significance level. An interim analysis, performed after enrollment of half of the intended patients, concluded that we had enough data to infer that silicone breast implants and other inflammatory conditions could increase the risk of fetal growth restriction, with SBI being associated with early-onset FGR. At that moment, we decided to publish a preliminary report of 38 pregnancies.

Results

Baseline characteristics

A total of 42 normotensive patients with growth-restricted pregnancies were sequentially approached and all provided written informed consent. One baby was born with Edwards' syndrome (trisomy 18), one mother was diagnosed with diabetes mellitus and two mothers were lost to follow-up.

Twelve (32%) of the 38 participants underwent cosmetic breast augmentation 4–18 years before FGR diagnosis (95% confidence interval [CI], 7–9 years). The mean volume of the prostheses was 278 ± 64 ml.

The mean age of the FGR+SBI mothers at inclusion was 36 ± 5 years and of the FGR–SBI mothers, 36 ± 6 years (Table 1). Twelve FGR+SBI (100%) and 23 FGR–SBI mothers (88%) were Caucasians. The FGR–SBI group also included two Asians (8%) and one black (4%) subject. Two FGR+SBI patients (5%) were overweight in the first prenatal consultation, all the others had normal weight. All mothers denied exposure to tobacco smoke, illicit drugs or alcohol, since the beginning of pregnancy.

The eight multiparous women in the FGR+SBI group had 25 previous pregnancies, comprising 19 miscarriages (76%), one fetal demise associated with FGR (4%), and five live births (16%), including one small-for-gestational age (4%) and four appropriate-for-gestational age infants (16%). The 13 multiparous women in the FGR–SBI group had 37 previous pregnancies, with 28 early miscarriages (75%), four pregnancies complicating with FGR leading to fetal demise (11%), and five live births, four small-for-gestational age children (11%) and one appropriate-for-gestational age infant (3%). There were 23 implantation failures of euploid

Table 1 Sample characteristics

	FGR+SBI (n = 12)	FGR – SBI (n = 26)	P value
Age, mean (standard deviation), years	36 ± 5	36 ± 6	NS
Race			
Caucasians	12 (100%)	23 (88%)	NS
Asians		2 (8%)	NS
Black		1 (4%)	NS
Body mass index classification			
Normal weight	10 (83%)	26 (100%)	NS
Overweight	2 (17%)		NS
Multiparous women	8	13	
Previous pregnancies	25	37	
Early miscarriages	19 (76%)	28 (75%)	NS
Fetal demise with growth restriction	1 (4%)	4 (11%)	NS
Small-for-gestationalage infants	1 (4%)	4 (11%)	NS
Appropriate-for-gestational age infants	4 (16%)	1 (3%)	NS
Index pregnancy			
Early FGR	11 (92%)	14 (54%)	0.03
Gestational age at FGR diagnosis, weeks	27 (95% CI, 25 to 30)	30 (95% CI, 29 to 32)	0.02
Estimated fetal weight % at diagnosis	6 (95% CI, 4 to 8)	7 (95% CI, 6 to 8)	NS
Severe FGR	3 (25%)	2 (8%)	NS

FGR+SBI, mothers with fetal growth restricted pregnancies and silicone breast implants; FGR–SBI, mothers with fetal growth restricted pregnancies, without silicone breast implants; NS, non-significant; 95% CI, 95% confidence interval

embryos in the FGR+SBI group and 14 in the FGR–SBI group.

None of the FGR+SBI patients fulfilled major clinical criteria for ASIA syndrome, such as myalgia, myositis or muscle weakness, arthralgia, arthritis, chronic fatigue, neurological manifestations, cognitive impairment or sicca syndrome.

Five FGR–SBI mothers were on prophylactic low-molecular-weight heparin from the beginning of pregnancy. One of them had positive lupus anticoagulant, two had previous growth-restricted stillbirths, one – with a negative thrombophilia workup – had a pulmonary embolism five years before the index pregnancy, and one had a family history of deep vein thrombosis. None of the FGR+SBI mothers was receiving prophylactic anticoagulation. Two FGR+SBI women were heterozygous for factor V Leiden and one was heterozygous for prothrombin 20,210 mutation. One FGR–SBI mother was heterozygous for factor V Leiden. None of the participants with inherited thrombophilia had autoantibodies.

A total of 22 patients had been screened for thrombophilia before pregnancy, either because of adverse pregnancy events or due to a personal or family history of thromboembolism. The remaining 16 were tested for thrombophilia at the time of FGR diagnosis.

All patients had normal homocysteine, prolactin, and vitamin D levels. Two FGR–SBI mothers (8%) with positive anti-thyroid peroxidase antibodies were taking thyroid hormones, none of the patients had anti-thyroglobulin antibodies.

The impact of silicone breast prostheses and autoantibodies on FGR

FGR+SBI patients had twice the prevalence of antinuclear antibodies ≥ 1:160 than FGR–SBI ones, respectively 50% (four speckled, two anti-centromere) and 23% (all speckled) (Table 2). Two FGR–SBI subjects (8%) had anti-thyroid peroxidase antibodies ≥ 1:640 and one (4%) had lupus anticoagulant. Four FGR+SBI (25%) and seven FGR–SBI (27%) mothers had antinuclear antibodies ≥ 1:320. The frequency of high-titer antinuclear or anti-thyroid peroxidase antibodies (≥ 1:320) was similar in both groups, 33% and 31%.

Silicone breast prostheses were associated with a 70% increased risk of early FGR (95% CI, 1.2–2.5; P = 0.02) (Table 2). FGR was diagnosed significantly earlier in the FGR+SBI than in the FGR–SBI group, respectively at 27 (95% CI, 25–30) and 30 weeks gestation (95% CI, 29–32). The estimated fetal weight percentile at diagnosis was 6 (95% CI, 4 to 8) in the FGR+SBI group and 7 (95% CI, 6–8) in the FGR–SBI group. Silicone breast prostheses also tripled the risk of severe FGR (95% CI, 0.62– 17).

Inflammatory conditions that might have contributed to placental insufficiency

Two thirds of the FGR+SBI participants and 58% of the FGR–SBI subjects had either a current or a recent infection. Half of the FGR+SBI and 39% of the FGR–SBI mothers were diagnosed with giardiasis. Intestinal dysbiosis was detected in 20% of the FGR+SBI and in 23% of the FGR–SBI group. A total of 17% of the FGR+SBI and 4% of the FGR–SBI women had chronic vaginal candidiasis, and 8% of FGR–SBI patients had chronic sinusitis. The prevalence of a Covid-19 infection within one month prior to the diagnosis of FGR was similar in the two groups, 8%. A FGR–SBI mother presented with toxoplasmosis seroconversion at 28 weeks of pregnancy, which was attributed to the immunosuppression that accompanies chronic anxiety and insomnia, two conditions characterized by hypercortisolism. Her neonate had no clinical signs of congenital toxoplasmosis and both IgM and IgG antibodies were negative. Complaints of extreme fear, usually of losing the baby, were similar in the two groups, 58%.

One FGR+SBI mother received hyaluronic acid injections and 60 units of botulinum toxin during pregnancy. The next day, she presented with livedo reticularis. Four weeks later, when her offspring was diagnosed with FGR, her C-reactive protein levels were 10.5 mg/L.

Forty-two percent of the participants (half of the FGR+SBI group and 38% of the FGR-SBI group) had antinuclear antibodies ≥ 1:160, anti-thyroid peroxidase antibodies ≥ 1:640 or positive lupus anticoagulant. One third of each group had high-titer antibodies.

Non-inflammatory conditions that might have contributed to placental insufficiency

A sedentary lifestyle throughout pregnancy was reported by 92% of the FGR+SBI and 85% of the FGR–SBI mothers, with most of them informing to rest as much as possible. Excessive weight gain (e.g. ≥ 1.5 kg per four weeks until 20 weeks' gestation), due to the consumption of a high-carbohydrate diet or binge eating, was 3.4 times more common (95% CI, 1.8–6.6) in FGR+SBI than in FGR–SBI women. The prevalence of thrombophilia was three times higher in FGR+SBI (25%) than in FGR-SBI patients (8%).

Discussion

Mechanisms involved in inflammation-related placental insufficiency

Early FGR represented 66% of the whole sample and 92% of the FGR+SBI group, much more prevalent than that reported in the literature, 20–30% [24]. Assuming

Table 2 Conditions that might have contributed to placental insufficiency

	FGR + SBP (n = 12)	FGR–SBP (n = 26)	P value
Inflammatory conditions			
Extreme fear	7 (58%)	15 (58%)	NS
Recent or current infection*	8 (67%)	15 (58%)	NS
Giardiasis, manifesting as lactose intolerance	6 (50%)	10 (38%)	NS
Chronic vaginal candidiasis	2 (17%)	1 (4%)	NS
Chronic sinusitis	0	2 (8%)	NS
Covid-19 infection	1 (8%)	2 (8%)	NS
Reactivated toxoplasmosis in the setting of long-term anxiety and insomnia, no signs of congenital toxoplasmosis	0	1 (4%)	NS
Recent filling and botulinum toxin with C-reactive protein levels of 10.5 mg/L	1 (8%)	0	NS
Autoantibodies	6 (50%)	10 (38%)	NS
Antinuclear antibodies	6 (50%)	7 (26%)	NS
High-titer antibodies	4 (33%)	8 (31%)	NS
Anti-thyroid peroxidase antibodies	0	2 (8%)	NS
Lupus anticoagulant (primary antiphospholipid syndrome)	0	1 (4%)	NS
Non-inflammatory conditions			
Sedentary status (< 40 min per day with physical activity)	11 (92%)	22 (85%)	NS
Excessive weight gain (e.g. > 1.5 kg/4 weeks during the first half of pregnancy), a surrogate of a high-carbohydrate diet	11 (92%)	7 (27%)	< 0.01
Inherited or acquired thrombophilia	3 (25%)	2 (8%)	NS

FGR+SBI, fetal growth restriction, mothers with silicone breast implants; FGR–SBI, fetal growth restriction, mothers without silicone breast implants; NS, non-significant; *Some women had more than one infection

inflammation and autoimmunity to have a role in FGR, it is possible that three inflammatory conditions present before pregnancy, namely silicone breast prostheses, giardiasis, and autoantibodies have contributed to anticipate the onset of FGR in our cohort.

In this study, all participants had two to four inflammatory conditions, such as SBI, extreme fear, infections, recent use of dermal fillers and botulinum toxin, intestinal or vaginal dysbiosis or autoantibodies. Positive antinuclear antibodies have been reported in the general population, but usually in a titer ≤ 1:80 [26]. A study including 100 women with recurrent pregnancy losses and 194 controls identified antinuclear antibodies ≥ 160 in 11% of the women with recurrent miscarriages and none of the controls [26], suggesting that these antibodies may harm the placenta.

One would expect systemic inflammation to cause placental insufficiency through a mechanism involving placental inflammation, but this seldom occurs. In a study of 184 normotensive fetal growth restricted pregnancies, only 1% of the placentas showed mononuclear cell infiltration [27]. Instead, the usual placental findings in FGR are reduced villous branching and failure to increase vessel diameter [28]. Placental vascular development, required to match fetal growth, depends on the activation of growth factors and proteolysis of the extracellular matrix.

Fibrinolytic enzymes, such as tissue plasminogen activator (tPA) have a crucial role in placental vascular modifications, by activating growth factors and mediating extracellular matrix proteolysis [29]. Cytokines stimulate the production of the most potent tPA inhibitor: plasminogen activator inhibitor (PAI)-1, the same occurring with increased levels of angiotensin or cortisol, which are also risk factors for FGR [30] (Fig. 1). A study demonstrated that PAI-1 levels in umbilical cord blood of normotensive FGR pregnancies were approximately tenfold higher than in controls [31], reinforcing the idea that reduced fibrinolytic activity mediates defective placental development.

Impact of silicone breast implants on gestational age and weight centile at FGR diagnosis

In this study, the presence of silicone breast prostheses anticipated the onset of FGR in three weeks, an insignificant period of time in extrauterine life, but not in intrauterine life. Anticipating delivery in three weeks may have dramatic consequences for neonatal morbidity and mortality. A study conducted in the US showed that among babies delivered from 26 to 32 weeks' gestation, each additional week in utero reduced the length of neonatal hospitalization by a minimum of 8 days [32]. In that study, 159 babies were

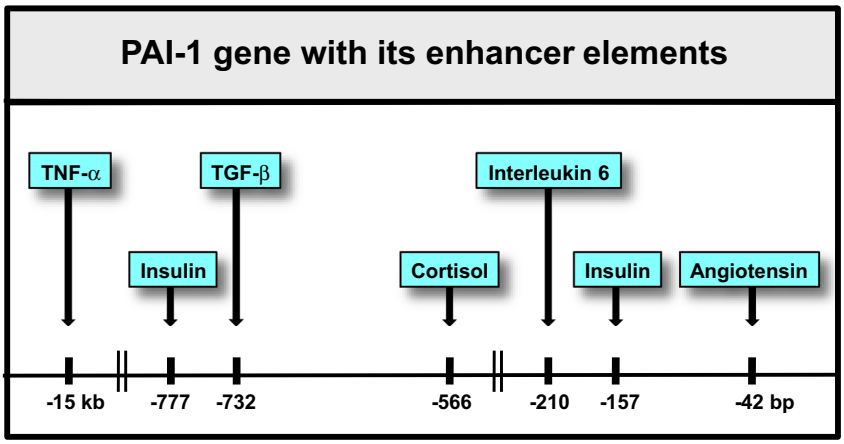

Fig. 1 Risk factors for fetal groth restriction converge to reduced fibrinolytic activity. PAI-1, plasminogen activator inhibitor-1; TNF-α: tumor necrosis factor-α; TGF-β: transforming growth-β

born at 27 weeks' gestation: 57% of them were intubated for ventilation, their mean length of hospital stay was 66 days and the mortality rate was 40%. Of the 262 babies born at 30 weeks' gestation, 21% were intubated for ventilation, their mean length of hospital stay was 40 days and the mortality rate was 13%. Of the 639 babies born at 33 weeks' gestation, 3% were intubated for ventilation, their mean length of hospital stay was 15 days and the mortality rate was 1%.

An unexpected finding in the present study was a significantly higher prevalence of excessive weight gain during pregnancy in the FGR+SBI group than in the FGR–SBI group (92% vs 27%, $P < 0.01$). One possible explanation is that women who undergo breast augmentation tend to control body weight through exercise and healthy diets. Many FGR+SBI women believed that during pregnancy they could eat twice as much as before pregnancy and rest as much as possible. Excessive weight gain is associated with high-carbohydrate diets, which stimulate insulin oversecretion. Insulin impairs fibrinolytic activity by increasing PAI-1 levels [33].

Future work

Five mothers (13%) from our cohort were on prophylactic low-molecular-weight heparin when FGR was diagnosed. The lack of benefit of heparin prophylaxis in the prevention of FGR found in our sample is in accordance with the results of a meta-analysis of eight trials including 963 women, 42% of whom had thrombophilia, randomized to prophylactic low-molecular-weight heparin or no anticoagulation [34]. Assuming that hypofibrinolysis is an important element in the pathogenesis of FGR, it remains to be elucidated whether medications that increase fibrinolytic activity, such as full-dose heparin or sertraline [35], can improve fetal growth and prolong pregnancy. Clinical trials have supported the safety of sertraline in pregnancy, as well as the efficacy of this mood-stabilizer in reducing binge eating frequency [36].

Our findings suggest that patients with lactose intolerance willing to conceive be screened for giardiasis. Metronidazole is the drug of choice for *Giardia* infection, but based on some reports of metronidazole teratogenicity [37] it is advised to treat giardiasis before pregnancy. Further studies are needed to clarify whether hydroxychloroquine can prevent silicone breast implant-related FGR and delay delivery until term. Notably, hydroxychloroquine is effective against metronidazole-resistant *Giardia* [38].

Limitations

As our results were obtained from a small cohort of patients, they should be considered preliminary. In order to better understand how SBI influence fetal growth, a large cohort of pregnant women with SBI should be screened for FGR, with the results compared to those of matched controls.

Conclusions

Our findings are consistent with the hypothesis that placental insufficiency may result from the association of inflammatory conditions, such as SBI, giardiasis, autoantibodies, and fear, with SBI significantly increasing the risk of early-onset FGR. Excessive weight gain was highly prevalent among FGR+SBI mothers, suggesting that lifestyle modifications may help prevent FGR related to SBI. We recommend that women with lactose intolerance willing to conceive be screened for giardiasis. Based on some reports of metronidazole teratogenicity, it is advised to treat giardiasis before pregnancy. Studies with large samples are needed to validate our findings and define whether silicone-related fetal growth restriction should be included in ASIA criteria.

Acknowledgements The author would like to express her deepest gratitude to Prof. Yehuda Shoenfeld, Prof. Luis Jarra, Dr. Daphne Sarah Usiglio, Dr. Jacqueline A. Menezes, Mrs. Tara Mizrachi, and the four referees for their valuable suggestions and critical review of the manuscript.

Funding The author received no financial support for thisresearch.

Compliance with ethical standards

Disclosures None.

References

1. Zur RL, Parks WT, Hobson SR (2020) The placental basis of fetal growth restriction. Obstet Gynecol Clin 47:81–98
2. Nardozza LMM, Caetano ACR, Zamarian ACP, Mazzola JB, Silva CP, Marçal VMG, Lobo TF, Peixoto AB, Araujo E Jr (2017) Fetal growth restriction: current knowledge. Arch Gynecol Obstet 295:1061–1077
3. Figueras F, Gratacos E (2017) An integrated approach to fetal growth restriction. Best Pract Res Clin Obstet Gynaecol 38:48–58
4. Sharma D, Shastri S, Sharma P (2016) Intrauterine growth restriction: antenatal and postnatal aspects. Clin Med Insights: Pediatr 10:67–83
5. Gourvas V, Dalpa E, Konstantinidou A, Vrachnis N, Spandidos DA, Sifakis S (2012) Angiogenic factors in placentas from pregnancies complicated by fetal growth restriction. Mol Med Rep 6:23–27
6. Cai E, Czuzoj-Shulman N, Abenhaim HA (2021) Maternal and fetal outcomes in pregnancies with long-term corticosteroid use. J Matern Fetal Neonatal Med 34:1797–1804
7. Infante-Rivard C, Rivard GE, Yotov WV, Génin E, Guiguet M, Weinberg C, Gauthier R, Feoli-Fonseca JC (2002) Absence of association of thrombophilia polymorphisms with intrauterine growth restriction. N Engl J Med 347:19–25
8. McCowan LM, Craige S, Taylor RS, Ward C, McLintock C, North RA (2003) Inherited thrombophilias are not increased in "idiopathic" small-for-gestacional-age pregnancies. Am J Obstet Gynecol 188:981–985
9. Al-Azemi M, Raghupathy R, Azizieh F (2017) Pro-inflammatory and anti-inflammatory cytokine profiles in fetal growth restriction. Clin Exp Obstet Gynecol 44:98–103
10. Amegah AK, Quansah R, Jaakkola JJ (2014) Household air pollution from solid fuel use and risk of adverse pregnancy outcomes: a systematic review and meta-analysis of the empirical evidence. PLoS ONE 9:e113920
11. Gomes J, Au F, Basak A, Cakmak S, Vincent R, Kumarathasan P (2019) Maternal blood biomarkers and adverse pregnancy outcomes: a systematic review and meta-analysis. Crit Rev Toxicol 49:461–478
12. Huang QT, Hang LL, Zhong M, Gao YF, Luo ML, Yu YH (2016) Maternal HCV infection is associated with intrauterine fetal growth disturbance: a meta-analysis of observational studies. Medicine 95:e4777
13. Østensen M, Andreoli L, Brucato A, Cetin I, Chambers C, Clowse ME, Costedoat-Chalumeau N, Cutolo M, Dolhain R, Fenstad MH, Förger F (2015) State of the art: reproduction and pregnancy in rheumatic diseases. Autoimmun Rev 14:376–386
14. Takeuchi N, Ekuni D, Irie K, Furuta M, Tomofuji T, Morita M, Watanabe T (2013) Relationship between periodontal inflammation and fetal growth in pregnant women: a cross-sectional study. Arch Gynecol Obstet 287:951–957
15. ISAPS – International Society of Aesthetic Plastic Surgery. International survey on aesthetic/cosmetic procedures performed in 2020. https://isaps.org/media/dzjfg50s/isaps-global-survey_2020.pdf. Accessed 29 May 2023
16. Soriano A, Butnaru D, Shoenfeld Y (2014) Long-term inflammatory conditions following silicone exposure: the expanding spectrum of the autoimmune/inflammatory syndrome induced by adjuvants (ASIA). Clin Exp Rheumatol 32:151–154
17. Colaris MJ, de Boer M, van der Hulst RR, Cohen Tervaert JW (2017) Two hundreds cases of ASIA syndrome following silicone implants: a comparative study of 30 years and a review of current literature. Immunol Res 65:120–128
18. Goren I, Segal G, Shoenfeld Y (2015) Autoimmune/inflammatory syndrome induced by adjuvant (ASIA) evolution after silicone implants. Who is at risk? Clin Rheumatol 34:1661–1666
19. Chen J, Zhu XM, Huynh MN, McRae M (2023) Breastfeeding outcome and complications in women with breast implants: A systematic review and meta-analysis. Aesthet Surg J. https://doi.org/10.1093/asj/sjad027
20. Coroneos CJ, Selber JC, Offodile AC, Butler CE, Clemens MW (2019) US FDA breast implant postapproval studies: long-term outcomes in 99,993 patients. Ann Surg 269:30–36
21. Taghipour A, Ghodsian S, Jabbari M, Olfatifar M, Abdoli A, Ghaffarifar F (2021) Global prevalence of intestinal parasitic infections and associated risk factors in pregnant women: a systematic review and meta-analysis. Trans R Soc Trop Med Hyg 115:457–470
22. Sengupta P, Chakraborty A (2023) Infection of the gastrointestinal tract: Giardiasis and amoebiasis. In: Viral, Parasitic, Bacterial, and Fungal Infections pp 365–373. Academic Press. https://doi.org/10.1016/B978-0-323-85730-7.00013-8
23. He X, Li Z, Li X, Zhao H, Hu Y, Han W, Wang C, Yin C, Chen Y (2023) The fecal microbiota of gravidas with fetal growth restriction newborns characterized by metagenomic sequencing. Curr Res Transl Med 71:103354
24 Dall'Asta A, Brunelli V, Prefumo F, Frusca T, Lees CC (2017) Early onset fetal growth restriction. Matern Health Neonatol Perinatol 3:2
25. Moons WG, Eisenberger NI, Taylor SE (2010) Anger and fear responses to stress have different biological profiles. Brain Behav Immun 24:215–219
26. Ticconi C, Rotondi F, Veglia M, Pietropolli A, Bernardini S, Ria F, Caruso A, Di Simone N (2010) Antinuclear autoantibodies in women with recurrent pregnancy loss. Am J Reprod Immunol 64:384–392
27. Paules C, Youssef L, Rovira C, Crovetto F, Nadal A, Peguero A, Figueras F, Eixarch E, Crispi F, Miranda J, Gratacós E (2019) Distinctive patterns of placental lesions in pre-eclampsia vs small for gestational age and their association with fetoplacental Doppler. Ultrasound Obstet Gynecol 54:609–616
28. Salafia CM, Charles AK, Maas EM (2006) Placenta and fetal growth restriction. Clin Obstet Gynecol 49:236–256
29. Milenkovic J, Milojkovic M, Stoimenov TJ, Djindjic B, Miljkovic E (2017) Mechanisms of plasminogen activator inhibitor 1 action in stromal remodeling and related diseases. Biomed Pap Med Fac Univ Palacky Olomouc Czech Repub 161:339–347
30. Morrow GB, Whyte CS, Mutch NJ (2021) A serpin with a finger in many PAIs: PAI-1's central function in thromboinflammation and cardiovascular disease. Front Cardiovasc Med 8:653655
31. Seferovic MD, Gupta MB (2016) Increased umbilical cord PAI-1 levels in placental insufficiency are associated with fetal hypoxia and angiogenesis. Dis Markers 7124186. https://doi.org/10.1155/2016/7124186

32. Manuck TA, Rice MM, Bailit JL, Grobman WA, Reddy UM, Wapner RJ, Thorp JM, Caritis SN, Prasad M, Tita AT, Saade GR, Sorokin Y, Rouse DJ, Blackwell SC, Tolosa JE, for the Eunice Kennedy Shriver National Institute of Child Health and Human Development Maternal-Fetal Medicine Units (MFMU) Network (2016) Preterm neonatal morbidity and mortality by gestational age: a contemporary cohort. Am J Obstet Gynecol 215:103.e1–103.e-14.
33. Nordt TK, Sawa H, Fujii S, Sobel BE (1995) Induction of plasminogen activator inhibitor type-1 (PAI-1) by proinsulin and insulin in vivo. Circulation 91:764–770
34. Rodger MA, Gris JC, De Vries JI, Martinelli I, Rey É, Schleussner E, Middeldorp S, Kaaja R, Langlois NJ, Ramsay T, Mallick R (2016) Low-molecular-weight heparin and recurrent placenta-mediated pregnancy complications: a meta-analysis of individual patient data from randomised controlled trials. Lancet 388:2629–2641
35. Hoirisch-Clapauch S (2022) Mechanisms affecting brain remodeling in depression: do all roads lead to impaired fibrinolysis? Mol Psychiatry 27:525–533
36. McElroy SL, Casuto LS, Nelson EB, Lake KA, Soutullo CA, Keck PE Jr, Hudson JI (2000) Placebo-controlled trial of sertraline in the treatment of binge eating disorder. Am J Psychiatry 157:1004–1006
37. Ajiji P, Uzunali A, Ripoche E, Vittaz E, Vial T, Maison P (2021) Investigating the efficacy and safety of metronidazole during pregnancy; A systematic review and meta-analysis. Eur J Obstet Gynecol Reprod Biol X 11:100128
38. Escobedo AA, Hanevik K, Almirall P, Cimerman S, Alfonso M (2014) Management of chronic Giardia infection. Expert Rev Anti Infect Ther 12:1143–1157