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Reproductive sequelae of parental severe illness before the pandemic: implications for the COVID-19 pandemic

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Objective: To investigate, with pre–COVID-19 data, whether parental exposure to severe systemic infections near the time of conception is associated with pregnancy outcomes.
Design: Retrospective cohort study.
Setting: Population-based study covering births within the United States from 2009 to 2016.
Participants: The IBM MarketScan Research database covers reimbursed health care claims data on inpatient and outpatient encounters that are privately insured through employment-sponsored health insurance. Our analytic sample included pregnancies to paired fathers and mothers.
Interventions(s): Parental preconception exposure (0–6 months before conception) to severe systemic infection (e.g., sepsis, hypotension, respiratory failure, critical care evaluation).
Main Outcome Measure(s): Preterm birth (i.e., live birth before 37 weeks) and pregnancy loss.
Result(s): A total of 999,866 pregnancies were recorded with 214,057 pregnancy losses (21.4%) and 51,759 preterm births (5.2%). Mothers receiving intensive care in the preconception period had increased risk of pregnancy loss, as did fathers. Mothers with preconception sepsis had higher risk of preterm birth and pregnancy loss, and paternal sepsis exposure was associated with an increased risk of pregnancy loss. Similar results were noted for hypotension. In addition, a dose response was observed for both mothers and fathers between preconception time in intensive care and the risk of preterm birth and pregnancy loss.
Conclusion(s): In a pre–COVID-19 cohort, parental preconception severe systemic infection was associated with increased odds of preterm birth and pregnancy loss when conception was soon after the illness. (Fertil Steril® 2020;114:1242–9. ©2020 by American Society for Reproductive Medicine.)
El resumen está disponible en Español al final del artículo.

Key Words: COVID-19, preconception health, pregnancy outcomes, severe illness, critical illness

Since its emergence in December 2019, severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has caused at least 4 million infections with more than 250,000 deaths globally (1). As the pandemic unfolds, the medical community continues to explore the sequelae of infection. The short- and long-term impact of coronavirus disease 2019 (COVID-19) on individuals, particularly regarding fertility, is currently unknown in terms of both direct damage done by the virus and related systemic illness. Case reports have shown that COVID-19 infection during pregnancy may lead to adverse birth outcomes, and studies suggest that coronaviruses may adversely affect pregnant women, but any effects of severe systemic infection unrelated to the virus are unknown (2, 3). Indeed,

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while some data suggest fever may affect fertility, less is known about the potential for reproductive harm from sepsis, hypotension, and respiratory failure (4).

Knowledge of the reproductive sequelae of severe systemic illness is needed beyond the COVID-19 pandemic and could be applied to other infections. Severe systemic illness can lead to effects through a variety of mechanisms, including generalized deconditioning, cognitive decline, increased postdischarge mortality, and cardiovascular disease (5–8). The mechanisms of reproductive impairments may include a direct toxic effect of the infection or treatment, ischemic effect through hypotension, or disruption in endocrine signaling critical to conception. Such effects could impair gamete quality in both parents or uterine competences in mothers.

Thus, aspects surrounding severe systemic infection and respiratory failure present unknown reproductive risks during the current pandemic. We therefore sought to examine the impact that severe systemic illness may have on pregnancy outcomes (e.g., preterm birth and pregnancy loss) when parents are exposed during the preconception period. We hypothesized that parents who suffered from recent severe systemic illness before conception may have adverse pregnancy outcomes.

METHODS

Study Cohort

The IBM MarketScan Research database was used for our study cohort. This database provides reimbursed health care claims data on inpatient and outpatient encounters covering more than 150 million individuals who are privately insured through employment-sponsored health insurance and Medicare coverage as supplement. We analyzed claims data from the years 2007–2016. Institutional review board approval was not required for the analysis, because this dataset contains deidentified patient information.

Cohort assembly and outcome ascertainment was based on the previously described methodology of Ailes et al. and Wall-Weiler et al. (9, 10). Briefly, pregnant women aged 20–45 years were identified from inpatient and outpatient files. Mothers, fathers, and infants were linked by means of family ID. Through member enrollment files, we verified babies' records using the estimated birth date and enrollment start date. To determine adjudicated gestational age we used International Classification of Diseases (ICD), Current Procedure Terminology (CPT), and Diagnosis-Related Group (DRG) codes according to the aforementioned methodology of Ailes et al. and Wall-Weiler et al. from inpatient and outpatient files from both mothers and newborns (9, 11, 12). The relevant codes are listed in Supplemental Table 1 (available online at www.fertstert.org). The medical records of mothers and fathers were obtained by inpatient and outpatient claims files. We included only those infants with one male and one female parent at birth. Mothers and fathers had to be enrolled in insurance plans associated with the database for at least 1 year before conception. Outcomes were identified via ICD-9/10 diagnosis and DRG codes from both in- and outpatient claims, as well as CPT codes from outpatient claims for the mother (see Supplemental Table 1).

Pregnancy Outcomes

Pregnancy outcomes analyzed in the study included live birth, stillbirth, ectopic pregnancy, induced abortion, spontaneous abortion, and preterm birth (<37 weeks). Pregnancy loss included ectopic pregnancies, abortions (induced and spontaneous), and stillbirths.

Parental Exposures

We initially identified parental (mother or father) exposure to severe illness related to infection (e.g., sepsis, hypotension, respiratory failure) in the 3 months before estimated conception. This time period was chosen because spermatogenesis takes ~3 months and therefore outcomes related to insults that occur during this time may be captured. A sensitivity analysis of up to 6 months before conception was also performed. Exposures related to severe systemic infection and respiratory failure were chosen based on those that have been reported for COVID-19 or influenza. Inpatient variables were examined concerning these outcomes using ICD-9/10, CPT, and DRG codes from 0 to 6 months before conception. The relevant exposure codes are listed in Supplemental Table 1 and included illness associated with sepsis/systemic inflammatory response syndrome, respiratory failure/acute respiratory distress syndrome, hypotension/shock, influenza, and critical care evaluation and management. Reference groups for relative risk (RR) were those individuals with no exposures.

Statistical Analysis

Descriptive statistics were presented as mean ± SD. Categoric variables were expressed as n (%). Differences in illness in both parents were examined with the use of chi-square or Fisher exact test as appropriate. Generalized estimating equation and generalized logit models estimated the RRs and corresponding 95% confidence intervals (CIs) of each outcome to allow for some families contributing subsequent births for binary and multinomial outcomes, respectively. All models were adjusted for birth year, region of care, and maternal factors including age, obesity, diabetes mellitus, hypertension, hyperlipidemia, and smoking. To evaluate unmeasured confounding effects, we calculated E-values, which estimates the minimum strength of association on the RR scale that an unmeasured confounder would need to have for both the exposure and the outcome to fully explain away a specific exposure-outcome association (https://www.evalue-calculator.com) (13). All tests were two sided and $P<.05$ was considered to be statistically significant. Analyses were done in SAS software version 9.4.

RESULTS

Study Cohort Demographics

In total, 999,866 pregnancies were observed during the study period, with 214,057 pregnancy losses (21.4%) and 51,759

TABLE 1

Paternal, maternal, and infant characteristics of cohort.

Characteristic	n (%)
Paternal age, y	
Mean ± SD	35.4 ± 5.4
<30	122035 (12.2)
30–39	674159 (67.4)
≥40	203692 (20.4)
Maternal, y	
Mean ± SD	33.2 ± 4.4
<30	213,175 (21.3)
30–39	698,707 (69.9)
≥40	88,004 (8.8)
Births	
Total	999,866
Live birth	785,809 (78.6)
Pregnancy loss	214,057 (21.4)
Preterm birth	51,759 (5.2)
Year of birth	
2009	107,287 (10.73)
2010	128,692 (12.87)
2011	158,069 (15.81)
2012	164,106 (16.41)
2013	134,818 (13.48)
2014	135,247 (13.53)
2015	90,747 (9.08)
2016	80,920 (8.09)
Region of childbirth	
Northeast	199,322 (19.93)
North Central	245,597 (24.56)
South	327,569 (32.76)
West	210,050 (21.01)
Unknown	17,348 (1.73)

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preterm births (5.2%) observed (Table 1). The mean paternal age was 35.4 years (SD 5.4) and mean maternal age was 33.2 years (SD 4.4).

Severe Systemic Infection and Preterm Birth/ Pregnancy Loss

Preconception respiratory/severe systemic infection in fathers and mothers was associated with preterm birth and pregnancy loss (Table 2). Any intensive care unit (ICU) admission in the 3 months before conception was associated with an increased risk of pregnancy loss for both mothers (RR 1.99, 95% CI 1.69–2.34) and fathers (RR 1.67, 95% CI 1.43–1.96). A sensitivity analysis for unmeasured confounding (i.e., E-value) determined that the minimum strength of association for an unmeasured confounder to explain away the identified associations between severe systemic infection and adverse pregnancy outcomes varied from 1.39 to 2.6 for men and from 1.51 to 3.39 for women. We next examined the RRs according to abortion types and did not identify differences between the two (Table 3). In addition, a longer stay in the ICU was associated for both mothers and fathers with a higher risk of preterm birth and pregnancy loss (Table 4).

Mothers and fathers with preconception sepsis were at higher risk of having a child with preterm birth (RR 1.61, 95% 1.02–2.54; RR 1.38, 95% CI 1.07–1.78; respectively) and fathers with preconception sepsis had a higher risk of pregnancy loss (RR 1.55, 95% CI 1.22–1.98). Those mothers with respiratory failure during the preconception period had a higher risk of pregnancy loss (RR 1.31, 95% CI 1.13–1.53). Mothers diagnosed with hypotension or shock in the preconception period had a higher risk of pregnancy loss (RR 1.99, 95% CI 1.69–2.34) as did fathers (RR 1.67, 95% CI 1.43–1.96). Furthermore, parents with multiple diagnoses of severe systemic illness (i.e., of sepsis, critical respiratory failure, hypotension/shock, and critical care evaluation) had higher risk of pregnancy loss though the sample size was small (Supplemental Table 2). Expanding the exposure interval up to 6 months did not meaningfully alter the results (Supplemental Table 3, available online at www.fertstert.org). The diagnosis of influenza during the preconception period for both mothers and fathers was not associated with a higher risk of preterm birth or pregnancy loss.

DISCUSSION

The reproductive sequelae of severe systemic illness are unknown, and understanding these are of particular importance during the COVID-19 pandemic. With the use of a U.S. claims cohort, the present report found that profound systemic infection before conception, in both fathers and mothers who were able to conceive soon after severe illness, was associated with higher RRs of pregnancy loss and preterm birth. Moreover, the higher the number and more severe the illnesses (e.g., respiratory failure, sepsis, ICU care), the higher the risk of these two adverse pregnancy outcomes.

Because SARS-CoV-2 can infect those of reproductive age, with most recovering, understanding the reproductive sequelae of the disease is important for counseling and aftercare of these patients as well as others with severe systemic infections. An estimated 5%–10% of COVID-19–positive patients require ICU admission and mechanical ventilation, which includes reproductive-age men and women (14–16). Severe systemic infection and its sequelae can put tremendous strain on an individual's body, which may affect health long after discharge, with deconditioning, muscle atrophy, cognitive decline, and increased mortality having been observed (5–7). In addition, those who survive sepsis may have an increased risk of early mortality, rehospitalization, emotional distress leading to anxiety and depression, and cardiovascular disease (8). However, the reproductive sequelae of recent preconception exposure to severe illness are unknown and also may apply to a subset of individuals who are able to conceive soon after such ailment.

We found that recent exposure to severe systemic infection in mothers or fathers is associated with adverse pregnancy outcomes such as preterm birth and pregnancy loss. The potential mechanisms that underlie these outcomes are unknown, but may include a direct effect of the infection and its consequences on reproductive organs or gametes (e.g., toxic or ischemic) or the side-effects of treatments during the illness. In addition, a disruption in endocrine signaling, which is critical for conception, may play a role. The underlying mechanisms are likely different in fathers versus mothers because there are likely carryover of these

TABLE 2

Risk of maternal and paternal preconception exposure (up to 3 months before conception) on preterm birth and pregnancy loss.

Diagnosis	All pregnancies (n = 999,866)	Full term (n = 734,050)	PTB (n = 51,759)	Pregnancy loss (n = 214,057)	SAB	TAB	PTB vs. full term		Pregnancy loss vs. LB	
							RR (95% CI)	E value (CI)[a]	RR (95% CI)	E value (CI)[a]
Sepsis										
Female	308	192 (62.3)	25 (8.1)	91 (29.6)	62 (20.1)	17 (5.5)	1.61 (1.02–2.54)	2.6 (1.16)	1.38 (1.07–1.78)	2.1 (1.34)
Male	315	196 (62.2)	19 (6.0)	100 (31.8)	67 (21.3)	21 (6.7)	1.24 (0.75–2.05)	1.79 (1.0)	1.55 (1.22–1.98)	2.47 (1.74)
Critical respiratory illness[b]										
Female	920	586 (63.7)	59 (6.4)	275 (29.9)	167 (18.2)	63 (6.9)	1.26 (0.95–1.67)	1.83 (1.0)	1.31 (1.13–1.53)	1.95 (1.51)
Male	1,142	769 (67.3)	71 (6.2)	302 (26.4)	196 (17.2)	56 (4.9)	1.20 (0.93–1.54)	1.69 (1.0)	1.13 (0.99–1.30)	1.51 (1.0)
Hypotension/shock										
Female	489	320 (65.4)	35 (7.2)	134 (27.4)	89 (18.2)	24 (4.9)	1.43 (0.97–2.09)	2.21 (1.0)	1.31 (1.07–1.61)	1.95 (1.34)
Male	358	243 (67.9)	17 (4.8)	98 (27.4)	64 (17.9)	22 (6.2)	0.92 (0.56–1.50)	1.39 (1.0)	1.31 (1.04–1.65)	1.95 (1.24)
Critical care evaluation										
Female	675	383 (56.7)	42 (6.2)	250 (37.0)	139 (20.6)	50 (7.4)	1.38 (0.99–1.92)	2.1 (1.0)	1.99 (1.69–2.34)	3.39 (2.77)
Male	714	436 (61.1)	44 (6.2)	234 (32.8)	139 (19.5)	59 (8.3)	1.30 (0.92–1.84)	1.92 (1.0)	1.67 (1.43–1.96)	2.73 (2.21)
Influenza										
Female	4,135	3,041 (73.5)	199 (4.8)	895 (21.6)	604 (14.6)	167 (4.0)	0.90 (0.78–1.05)	1.46 (1.0)	1.05 (0.97–1.13)	1.28 (1.0)
Male	4,460	3,317 (74.4)	195 (4.4)	948 (21.3)	656 (14.7)	156 (3.5)	0.82 (0.70–0.95)	1.74 (1.29)	1.03 (0.96–1.11)	1.21 (1.0)

Note: Results are presented as n (%) unless otherwise specified. Percentages may not add up to 100% owing to rounding. RRs adjusted for year of birth, maternal age, region of birth, and maternal factors including obesity, diabetes mellitus, hypertension, hyperlipidemia, and smoking. CI = confidence interval; RR = risk ratio; LB = live birth; PTB = preterm birth; RR = risk ratio; SAB = spontaneous abortion, TAB = therapeutic abortion.

[a] E values estimate the minimum strength of association on the risk ratio scale that an unmeasured confounder would need to have with both the exposure and the outcome to fully explain away a specific exposure-outcome association. The lowest possible E value is 1, meaning that no unmeasured confounding would explain the association.

[b] Acute respiratory failure, acute respiratory distress syndrome, acute on chronic respiratory failure.

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TABLE 3

Risk of maternal and paternal preconception exposure (up to 3 months before conception) on spontaneous and therapeutic abortion.

	SAB vs. LB		TAB vs. LB	
Diagnosis	**RR (95% CI)**	**E value (CI)[a]**	**RR (95% CI)**	**E value (CI)[a]**
Sepsis				
Female	1.43 (1.06–1.91)	2.21 (1.31)	1.30 (0.79–2.14)	1.92 (1.0)
Male	1.57 (1.19–2.07)	2.52 (1.67)	1.66 (1.06–2.60)	2.71 (1.31)
Critical respiratory illness[b]				
Female	1.23 (1.03–1.47)	1.76 (1.21)	1.42 (1.08–1.86)	2.19 (1.37)
Male	1.12 (0.95–1.31)	1.49 (1.0)	1.002 (0.76–1.32)	1.05 (1.0)
Hypotension/shock				
Female	1.30 (1.03–1.65)	1.92 (1.21)	1.24 (0.82–1.88)	1.79 (1.0)
Male	1.28 (0.98–1.68)	1.88 (1.0)	1.55 (0.99–2.41)	2.47 (1.0)
Critical care evaluation				
Female	1.66 (1.37–2.02)	2.71 (2.08)	2.09 (1.55–2.82)	3.6 (2.47)
Male	1.49 (1.23–1.81)	2.34 (1.76)	2.21 (1.68–2.93)	3.85 (2.75)
Influenza				
Female	1.04 (0.96–1.14)	1.24 (1.0)	1.09 (0.94–1.28)	1.4 (1.0)
Male	1.05 (0.97–1.15)	1.28 (1.0)	0.94 (0.80–1.11)	1.32 (1)

Adjusted for year of birth, maternal age, region of birth, and maternal factors including obesity, diabetes mellitus, hypertension, hyperlipidemia, and smoking. CI = confidence interval; LB = live birth; RR = risk ratio; SAB = spontaneous abortion; TAB = therapeutic abortion.

[a] E values estimate the minimum strength of association on the risk ratio scale that an unmeasured confounder would need to have with both the exposure and the outcome to fully explain away a specific exposure-outcome association. The lowest possible E value is 1, meaning that no unmeasured confounding would explain the association.

[b] Acute respiratory failure, acute respiratory distress syndrome, acute on chronic respiratory failure.

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effects into the pregnancy itself in mothers that may affect uterine or placental function.

Regarding fathers, the underlying mechanisms of severe systemic illness translating to adverse pregnancy outcomes likely involves a combination of direct pathogenic effects on the testes from either infection or treatment, ischemia, or disruption in the hypothalamic-pituitary-gonadal (HPA) axis. Indeed, acute illness may lead to disruptions in the HPA axis that can effect fertility and thereby may effect birth outcomes (17, 18). Systemic inflammation itself may also cause disruption in endocrine signaling or pathogenesis. Indeed, conditions with systemic inflammation have demonstrated increased risk of preterm birth in active disease (19). Moreover, high fevers from acute infection in men are also known to harm spermatogenesis (4). In addition, the epigenetic profile of sperm (e.g., DNA methylation, histone modification, and microRNA expression) may be altered by toxic exposures or illness (20–22). However, the increased risks of the adverse pregnancy outcomes observed in the present study may be due to the fact that those admitted to an ICU are more unhealthy at baselin,e and prior literature has suggested that poor preconception health can negatively affect perinatal outcomes (12).

Regarding mothers, the underlying mechanisms driving adverse pregnancy outcomes from a preconception exposure to severe illness are likely complex, because the exposures may extend into pregnancy itself. A direct toxic effect on gametes may also drive these effects in mothers, similarly to fathers. Preconception stress in forms other than an acute insult have been documented to adversely affect pregnancy outcomes such as from prenatally underweight mothers and psychosocial stress (23, 24). Stressful environments before conception may be independent from traditional social (e.g., alcohol, drugs) and medical (e.g., placental abnormalities, gestational hypertension) stresses, as suggested by these studies. Because the mechanisms through which maternal stress affects pregnancy are unknown, one can only postulate that these events may be driven by epigenetic changes

TABLE 4

Risk of maternal and paternal preconception ICU stay on preterm birth and pregnancy loss.

					PTB vs. full term		Pregnancy loss vs. full term	
ICU days	**All**	**Full term**	**PTB**	**Pregnancy loss**	**RR (95% CI)**	***P* trend**	**RR (95% CI)**	***P* trend**
Mother								
0	999,211	733,667 (73.4)	51,717 (5.2)	213,827 (21.4)	Ref.	0.002	Ref.	<.0001
1	592	346 (58.5)	35 (5.9)	211 (35.6)	1.27 (0.83–1.71)		1.88 (1.56–2.20)	
≥2	83	≥30 (44.6)	<11 (8.4)	39 (47.0)	2.32 (0.44–4.20)		2.83 (1.58–4.08)	
Father								
0	999,172	733,614 (73.4)	51,715 (5.2)	213,843 (21.4)	Ref.	0.02	Ref.	<.0001
1	626	386 (61.7)	≥30 (5.9)	203 (32.4)	1.24 (0.82–1.66)		1.65 (1.37–1.94)	
≥2	88	50 (56.8)	< 11 (8.0)	31 (35.2)	1.73 (0.36–3.10)		1.78 (0.98–2.57)	

Note: Percentages may not add to 100% owing to rounding. RRs adjusted for year of birth, maternal age, region of birth, and maternal factors including obesity, diabetes mellitus, hypertension, hyperlipidemia, and smoking. CI = confidence interval; ICU = intensive care unit; PTB = preterm birth; RR = risk ratio.

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induced by the event (25–27). In addition, preconception micronutrient deficiencies that may be induced by the event can lead to adverse birth outcomes (28).

A few additional limitations warrant mention. As with any database that relies on diagnosis and procedural codes, errors in coding may influence the results and, as such, specific details underlying a patient's comorbidities and treatments could not be ascertained. Furthermore, undersampling of diagnoses such as influenza may occur due to rule-out diagnoses in uninfected and true cases never seen in the health care setting, which would likely bias findings to the null. However, others have used similar techniques to identify influenza cases within the MarketScan database (29–33). The database is composed of individuals with commercial employment-based health insurance and thus may not be generalizable to other populations (34). For example, the frequency of preterm birth (preterm deliveries/all deliveries) was only 5.2%, which is significantly lower than the reported rate for the general population (35) In addition, early pregnancy losses from undetected pregnancies are not captured and therefore may alter observed results. Thus, the analysis applies only to couples who were able to have a recognized pregnancy following severe systemic illness. Next, we examined only couples who achieved pregnancy, and some exposed men and women may have been unable to conceive at all. In addition, many social determinants of health, which may represent confounders, were not available in the database (e.g., education, race/ethnicity, income, parity), which may influence the pregnancy-related outcomes. Similarly, several lifestyle factors (e.g., substance abuse) that also may influence outcomes were not available. Furthermore, conception dates were estimated, so that the exact timing of conception may not be precise. Finally, unmeasured confounding may persist which can influence reproductive outcomes (e.g., presence of an underlying chronic condition).

Nonetheless, preconception parental systemic illness near the time of conception may increase risks of preterm birth and pregnancy loss. By examining reproductive sequelae among subjects after exposure to severe systemic infection, the present study may be used to consider timing of pregnancy after recovery. However the findings must be regarded cautiously and considered to be hypothesis generating until they are further investigated prospectively. Although the RR is modest for most exposures (<1.5), it is significant, and future prospective studies should determine strategies to mitigate the observed risks.

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Secuelas reproductivas de enfermedad severa de los padres antes de la pandemia: implicaciones para la pandemia de COVID-19.

Objetivo: Investigar, con datos pre-COVID, si la exposición de los padres a infecciones sistémicas severas cerca del momento de la concepción está asociada a resultados gestacionales.

Diseño: Estudio retrospectivo de cohorte

Lugar: Estudio poblacional con cobertura de nacimientos en Estados Unidos entre 2009 y 2016.

Participantes: La base de datos de IBM MarketScan Research abarca datos de reclamos de salud reembolsados de pacientes hospitalizados y ambulatorios asegurados de forma privada a través de un programa de seguro médico patrocinado por el empleo. Nuestro análisis incluyó gestaciones de padres y madres emparejados.

Intervención(es): Exposición preconcepcional (0 a 6 meses antes de la concepción) de padres y madres a infección sistémica severa (ejemplo sepsis, hipotensión, fallo respiratorio, evaluación de cuidados críticos).

Medida(s) de resultado principal: Parto pretérmino (recién nacido vivo antes de 37 semanas) y pérdida gestacional.

Resultado(s): Un total de 999,866 gestaciones fueron registradas con 214,057 pérdidas gestacionales (21.4%) y 51,759 partos pretérmino (5.2%). Las madres que recibieron cuidados intensivos en el periodo preconcepcional presentaron un riesgo aumentado de pérdida gestacional, al igual que los padres. Las madres con sepsis preconcepcional tuvieron un riesgo mayor de nacimiento pretérmino y pérdida gestacional, y la exposición a sepsis en el padre se asoció a un riesgo aumentado de pérdida gestacional. Resultados similares se presentaron en hipotensión. Además, se observó una dosis-respuesta, tanto para los padres como para las madres, entre el tiempo en cuidados intensivos previo a la concepción y el riesgo de parto pretérmino y pérdida gestacional.

Conclusión(es): En una cohorte anterior al COVID-19, la infección sistémica grave en los padres antes de la concepción se asoció a un aumento de las posibilidades de parto pretérmino y pérdida gestacional cuando la concepción se produjo poco después de la enfermedad.