High-sensitivity C-reactive protein levels and pregnancy outcomes in women with unexplained infertility after ovarian stimulation with intrauterine insemination in a multicenter trial

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Objective: To determine if chronic inflammation, assessed by basal high-sensitivity C-reactive protein (hs-CRP) levels, is associated with pregnancy outcomes in women with unexplained infertility undergoing ovarian stimulation with intrauterine insemination.
Design: Prospective cohort analysis of the Reproductive Medicine Network's Assessment of Multiple Intrauterine Gestations from Ovarian Stimulation (AMIGOS) randomized controlled trial.
Setting: Multicenter university-based randomized controlled trial.
Patient(s): A total of 781 couples with unexplained infertility.
Intervention(s): Secondary analysis.
Main Outcome Measure(s): Adjusted risk ratios of live birth, clinical pregnancy, and pregnancy loss rates by hs-CRP levels.
Result(s): Associations between hs-CRP levels and clinical pregnancy rates were not observed after adjustment for baseline body mass index. There were fewer live births among women with higher hs-CRP levels, although confidence intervals crossed 1.0. The risk of pregnancy loss was greater in women with increased hs-CRP levels (1–3 mg/L: risk ratio [RR], 1.67; 95% confidence interval [CI], 1.00–2.79; >3–10 mg/L: RR, 1.84; 95% CI, 1.06–3.20; and >10 mg/L: RR, 2.14; 95% CI, 1.05–4.36 compared to women with hs-CRP <1 mg/L).
Conclusion(s): This investigation suggests that chronic inflammation may increase the risk of pregnancy loss but not impact the clinical pregnancy rate in women with unexplained infertility undergoing ovarian stimulation with intrauterine insemination. Associations between inflammation and pregnancy outcomes in women with infertility merit further investigation.
Clinical Trial Registration Number: clinicaltrials.gov NCT01044862. (Fertil Steril Rep® 2022;3:57–62. ©2022 by American Society for Reproductive Medicine.)
Key Words: Unexplained infertility, high-sensitivity C-reactive protein, ovarian stimulation, live birth, pregnancy loss

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Infertility affects approximately 10%–15% of couples attempting pregnancy. No readily identifiable cause is found for 15%–30% of couples following a standard evaluation, leading to a diagnosis of unexplained infertility (1). Chronic inflammation, frequently assessed by serum high-sensitivity C-reactive protein (hs-CRP) levels, has been linked to adverse reproductive outcomes, including reduced fecundability, recurrent miscarriage, and recurrent in vitro fertilization (IVF) failures (2, 3). The hs-CRP is an acute phase reactant protein released from the liver and serves as a marker to identify inflammation. It is used by some physicians as a component of routine cardiovascular disease risk assessment to identify those at high risk for adverse outcomes (such as heart attack and stroke) and to direct pharmacological therapy (4, 5). There are several factors known to be associated with higher baseline hs-CRP levels that may be associated with infertility, including obesity, endometriosis, and polycystic ovarian syndrome (6–8). While low-grade inflammation is found in 20%–40% of reproductive age women, hs-CRP is not a routine diagnostic or therapeutic marker used as part of an infertility evaluation (3). The prevalence of subclinical inflammation in women with unexplained infertility and the role of elevated hs-CRP levels in the prediction of treatment success following ovarian stimulation-intrauterine insemination (OS-IUI), typically the first-line treatment for unexplained infertility, remains unknown.

In addition to the evidence supporting an association between chronic inflammation and poorer reproductive outcomes, prior studies have also suggested that treating inflammation, as assessed by hs-CPR concentrations, may improve outcomes. The EAGeR trial was a randomized, double-blinded, controlled trial that included 1,228 fertile women with a history of one to two previous pregnancy losses. Low-dose aspirin (given to reduce subclinical inflammation) was compared to a placebo before conception. Preintervention hs-CRP levels were collected as a marker of chronic inflammation. The live birth and pregnancy loss rates were not different with aspirin (9). However, compliance with low-dose aspirin at least 5 days per week resulted in eight more human gonadotropin (hCG)-detected pregnancies (95% confidence interval [CI], 4.64–10.96 pregnancies), 15 more live births (95% CI, 7.65–21.15 births), and 6 fewer pregnancy losses (95% CI, −12.0 to −0.2 losses) for every 100 women, compared with placebo (10). Furthermore, women in the highest tertile of preconception, preintervention hs-CRP level $\geq$1.95 mg/L, who received placebo had a notably decreased live birth rate than women in the lower and middle tertiles. Those in the upper tertile who received aspirin improved their live birth rate similar to the lower and middle tertile groups (11). These findings suggest that chronic inflammation may negatively affect fertility. It also suggests that low-dose aspirin administrated to reduce chronic inflammation may improve reproductive outcomes in women with a history of past pregnancy loss.

The purpose of this study was to identify the prevalence of elevated hs-CRP levels and to determine their associations with treatment outcomes, including clinical pregnancy, live birth, and miscarriage rates, in women with unexplained infertility undergoing OS-IUI. We hypothesized that elevated levels would be associated with poorer reproductive outcomes.

MATERIALS AND METHODS

This is a secondary analysis of the Assessment of Multiple Intrauterine Gestations from Ovarian Stimulation (AMIGOS) study, which is a collaborative effort of the NICHD's Reproductive Medicine Network. The AMIGOS was conducted at 12 centers in the United States (clinicaltrials.gov NCT01044862) with the goal to determine the rate of multiple gestations among women with clinical pregnancies in couples with unexplained infertility treated with up to four cycles of ovarian stimulation with gonadotropin (n = 301), clomiphene (n = 300), or letrozole (n = 299) (12). Enrollment occurred between 2010 and 2014. The primary outcome was the multiple gestation rate, while secondary outcomes included the pregnancy rate, live birth rate, live birth rate of multiple gestational pregnancies, and time to pregnancy. Clinical pregnancy was defined as the presence of an intrauterine gestational sac(s) with positive fetal cardiac activity in at least one sac. Pregnancy loss was defined as a biochemical pregnancy or clinical pregnancy loss. Live birth was defined as the delivery of a live infant. Baseline reproductive and metabolic hormones, and other serum biomarkers, including hs-CRP, were collected in the early follicular phase before initiating treatment. Samples were collected at patients' respective clinic locations then shipped to a central laboratory (the Ligand Assay Core laboratory at the University of Virginia) for analysis. Serum hs-CRP levels (mg/L) were measured using an Immulite assay (Siemens Diagnostics, Los Angeles, CA). The assay sensitivity was 0.02 mg/dL, and the intra-assay and inter-assay coefficients of variation were 3.1 and 4.8, respectively (13).

Of the 870 patients completing at least one cycle of OS-IUI, 18 were excluded due to missing baseline hs-CRP serum measurements, 20 due to ectopic pregnancy, and 1 patient with an elective termination was omitted. Fifty patients with multiple gestation pregnancies were also excluded due to the known association of multiple gestation pregnancy with an increased risk of pregnancy loss (14). Thus, 781 patients were included in the analyses.

The hs-CRP concentrations were analyzed as categories, (<1 mg/L, 1–3 mg/L, >3–10 mg/L, and >10 mg/L). The hs-CRP categories are defined by the Center for Disease Control and American Heart Association guidelines regarding hs-CRP levels as a predictor of cardiovascular risk. The cut-points of <1 mg/L ("low risk"), 1.0–3 mg/L ("average risk"), and >3 mg/L ("high risk" of cardiovascular disease) correspond to the tertile distributions of >40,000 adult patients from a wide variety of populations of low, average, and high risk of cardiovascular disease (15, 16). The baseline characteristics by hs-CRP category are expressed as means with standard deviations or medians with interquartile ranges based on the distribution of the data. ANOVA with post hoc comparisons, Kruskal-Wallis, or χ^2 tests were used as appropriate to compare groups. A P value of $<.05$ was considered statistically significant.

Risk ratios (RR) and 95% CI for the outcomes of live birth, clinical pregnancy, and pregnancy loss were estimated using modified Poisson regression models with robust standard errors. Models examining associations between hs-CRP levels and pregnancy loss were restricted to participants who

TABLE 1

Baseline characteristics of 781 patients undergoing intrauterine insemination by hs-CRP concentration

Baseline characteristics	hs-CRP < 1 mg/L (n = 298)	hs-CRP 1–3 mg/L (n = 215)	hs-CRP >3–10 mg/L (n = 215)	hs-CRP >10 mg/L (n = 53)	Total (n = 781)	
	Mean (SD)	Mean (SD)	Mean (SD)	Mean (SD)	Mean (SD)	*P* value[a]
Age (y)	32.0 (4.1)	32.4 (4.3)	32.4 (4.3)	33.3 (4.3)	32.3 (4.2)	.18
Waist circumference (inches)	30.7 (4.5)	33.8 (5.1)	37.8 (6.4)	38.3 (7.2)	34.0 (6.2)	<.0001
Systolic blood pressure (mm Hg)	113.6 (11.8)	116.4 (12.1)	119.2 (13.3)	116.6 (12.2)	116.1 (12.5)	<.0001
Diastolic blood pressure (mm Hg)	72.2 (9.5)	74.9 (9.0)	77.2 (10.0)	76.2 (9.9)	74.6 (9.7)	<.0001
	Median (IQR)	Median (IQR)	Median (IQR)	Median (IQR)	Median (IQR)	*P* value[b]
Duration of infertility (mo)	24 (26)	24 (29)	25 (28)	24 (30)	24 (30)	.32
Body mass index (kg/m^2)	22.7 (4.9)	25.2 (6.5)	30.2 (8.8)	31.9 (13.4)	25.3 (8.3)	<.0001
Antimüllerian hormone (ng/mL)	2.2 (2.3)	2.4 (2.6)	2.0 (2.4)	1.8 (1.6)	2.1 (2.3)	.12
	n (%)	n (%)	n (%)	n (%)	n (% of total)	*P* value[c]
Race						.10
Non-Hispanic White	222 (74.5)	154 (71.6)	153 (71.2)	37 (69.8)	566 (72.5)	
Non-Hispanic Black	16 (5.4)	20 (9.3)	20 (9.3)	9 (17.0)	65 (8.3)	
Hispanic	27 (9.1)	25 (11.6)	21 (9.8)	6 (11.3)	79 (10.1)	
Other	33 (11.1)	16 (7.4)	21 (9.8)	1 (1.9)	71 (9.10)	
Income						.22
<$50,000	46 (15.4)	40 (18.6)	35 (16.3)	14 (26.4)	135 (17.3)	
≥$50,000	207 (69.5)	140 (65.1)	136 (63.3)	28 (52.8)	511 (65.4)	
Wish not to answer	45 (15.1)	35 (16.3)	44 (20.5)	11 (20.8)	135 (17.3)	
History of pregnancy loss						.58
Yes	65 (21.8)	42 (19.5)	46 (21.4)	15 (28.3)	168 (21.5)	
No	233 (78.2)	173 (80.5)	169 (78.6)	38 (71.7)	613 (78.5)	
History of live birth						.51
Yes	53 (17.8)	37 (17.2)	45 (20.9)	13 (24.5)	148 (19.0)	
No	245 (82.2)	178 (82.8)	170 (79.1)	40 (75.5)	633 (81.1)	
Treatment						.91
Clomiphene citrate	109 (36.6)	79 (36.7)	70 (32.6)	18 (34.0)	276 (35.3)	
Letrozole	96 (32.2)	70 (32.6)	80 (37.2)	17 (32.1)	263 (33.7)	
Gonadotropin	93 (31.2)	66 (30.7)	65 (30.2)	18 (34.0)	242 (31.0)	

Note: hs-CRP = high-sensitivity C-reactive protein; IQR = interquartile range.
[a] Analysis of variance.
[b] Kruskal-Wallis test.
[c] χ^2 test.

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achieved a pregnancy (excluding multiple gestation pregnancies), defined as an initial rise in hCG levels (n = 249). Factors evaluated as potential confounders included age (years), race/ethnicity (non-Hispanic White, non-Hispanic Black, Hispanic, other), treatment group (clomiphene citrate, letrozole, gonadotropins), income (<$50,000, ≥$50,000, prefer not to report), body mass index (BMI) (<18.5, 18.5–24.9, 25.0–29.9, ≥30), a history of pregnancy loss (yes, no), duration of infertility (≤12 months, 13–24 months, 25–36 months, >36 months), serum antimüllerian hormone levels (ng/mL), systolic and diastolic blood pressure (mm Hg), and waist circumference (cm) (17). Confounders were evaluated by estimating the change in the RRs for the hs-CRP levels when controlling the factor of interest. Potential confounders were evaluated individually and with the use of a manual backward selection approach. Only BMI met the criteria for confounding (defined as >10%

TABLE 2

Unadjusted and adjusted risk ratios and 95% confidence intervals for associations between hs-CRP and live birth, clinical pregnancy, and pregnancy loss outcomes among 781 patients with unexplained infertility

	Live birth[a]			Clinical pregnancy			Pregnancy loss		
hs-CRP categories	N	Unadjusted RR (95% CI)	Adjusted RR[b] (95% CI)	n	Unadjusted RR (95% CI)	Adjusted RR[b] (95% CI)	n	Unadjusted RR (95% CI)	Adjusted RR[b] (95% CI)
hs-CRP categories									
<1 mg/L	298	Ref	Ref	298	Ref	Ref	86	Ref	Ref
1–3 mg/L	215	1.00 (0.72–1.38)	0.91 (0.65–1.27)	215	1.12 (0.83–1.50)	1.07 (0.79–1.44)	75	1.57 (0.95–2.60)	1.67 (1.00–2.79)
>3–10 mg/L	215	0.92 (0.66–1.28)	0.74 (0.50–1.08)	215	1.03 (0.76–1.39)	0.91 (0.64–1.28)	68	1.60 (0.96–2.66)	1.84 (1.06–3.20)
>10 mg/L	53	0.99 (0.58–1.70)	0.79 (0.44–1.40)	53	1.15 (0.72–1.85)	1.01 (0.61–1.68)	20	1.81 (0.93–3.53)	2.14 (1.05–4.36)

Note: RR = risk ratio; CI = confidence interval; hs-CPR = high-sensitivity C-reactive protein.
[a] RRs and 95% CIs were calculated using generalized estimating equations to estimate modified Poisson regression models with robust standard errors.
[b] Model adjusted for body mass index (<18.5, 18.5–24.9 (reference), 25.0–29.9, ≥30).

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change in RR upon inclusion or removal from the model) in models assessing live birth, and therefore BMI was included in all adjusted models.

Using PASS 16 software (NCSS, LLC, Kaysville, Utah), power calculations for the sample of 781 patients indicated the study would have 80% power to detect a RR for live birth of 0.59 for hs-CRP ≥3.0, given a 5% type I error rate for false-positive conclusions (two-sided alpha = 0.05) and an R^2 of 0.2 for the degree of correlation between the hs-CRP levels and the other covariates. For these calculations, we assumed a 25% live birth rate among women with normal hs-CRP (<3.0 mg/L) corresponding to the birth rate observed in the AMIGOS trial and assumed a 30% prevalence of elevated hs-CRP given reports of low-grade inflammation in 20%–40% of reproductive age women (3). This study received approval from the University of Oklahoma Health Science Center's Institutional Review Board.

RESULTS

Of the 900 AMIGOS participants, 781 were included after the application of the exclusion criteria. The baseline measures of BMI, waist circumference, and blood pressure were greater among women with higher hs-CRP concentrations ($P<.0001$) (Table 1). The other baseline characteristics did not differ by hs-CRP category. Among the 781 participants undergoing OS-IUI treatment, 249 (31.9%) achieved a pregnancy, 201 (25.7%) had a confirmed clinical pregnancy, and 174 (22.3%) had a live birth. Among those who achieved a pregnancy, 77 (30.9%) experienced a biochemical or clinical pregnancy loss.

Elevated hs-CRP levels, defined as >3 mg/L based on cardiovascular risk, were observed in 34.3% (n = 268) of the participants. Fewer live births were noted with higher hs-CRP levels after adjusting for BMI; however, the CIs included the null value (Table 2). We found no evidence of an association between the basal hs-CRP levels and clinical pregnancy, with all risk ratios estimated near 1.0. Among women who achieved a pregnancy, the risk of pregnancy loss increased with increasing the hs-CRP levels (1–3 mg/L: RR, 1.67; 95% CI, 1.00–2.79; >3–10 mg/L: RR, 1.84; 95% CI, 1.06–3.20 and >10 mg/L: RR, 2.14; 95% CI, 1.05–4.36 compared with women with hs-CRP <1 mg/mL) (Table 2).

DISCUSSION

Chronic subclinical inflammation, as assessed by the elevated serum hs-CRP concentration, has been associated with adverse pregnancy outcomes in prior investigations, yet little is known about the prevalence of elevated hs-CRP levels in women with unexplained infertility or its relationship to outcomes of infertility treatments in this population (2, 3, 18). In the present study, we found that the risk of pregnancy loss was greater in women with unexplained infertility after OS-IUI when the hs-CRP levels were higher.

We determined that the prevalence of elevated hs-CRP levels (based on cardiovascular guidelines, i.e., >3 mg/L) in women with unexplained infertility was similar to other reports for reproductive-aged women in general at 34.3%. However, the varying characteristics among prior study populations make direct comparisons difficult (3). The expected prevalence of elevated hs-CRP concentrations in the general population ranges from 20%–40%, established from three data sets, including the BioCycle, EAGeR, and the NHANES cohorts (9, 19, 20). However, these prevalence calculations defined an elevated hs-CRP as a level ≥2 mg/L and excluded those ≥10 mg/L. The BioCycle and EAGeR specifically excluded women with infertility and showed a lower prevalence of elevated hs-CRP levels (20% and 30%, respectively) than the NHANES, which did not exclude women with infertility (prevalence of 40%). The NHANES also obtained hs-CRP levels irrespective of the menstrual cycle phase (20). It has been well documented that hs-CRP levels vary throughout natural menstrual cycles. The BioCycle study evaluated CRP levels among healthy, regularly menstruating women multiple times throughout the menstrual cycle. While this study used a different platform for the CRP measurements, the assay was sensitive to concentrations as low as 0.3 mg/L. They

found that the proportion of women with CRP levels >1 mg/L is greatest during menses and lowest during ovulation (19). Based on our findings, the prevalence of elevated hs-CRP in unexplained infertility is likely comparable with that of the general population.

There are only a few studies that have attempted to examine hs-CRP levels and IUI outcomes, and the findings are mixed. One small study (n = 63) compared the CRP levels between infertile patients undergoing OS-IUI who achieved pregnancy and those that did not. The levels were measured on the day of hCG trigger and 8 days post trigger and included patients with all infertility diagnoses. The patients who achieved pregnancy were noted to have significantly lower CRP levels on both the day of trigger (0.7 ± 0.5 vs. 2.2 ± 2.3 mg/L, P=.001) and 8 days after the hCG trigger (0.6 ± 0.4 vs. 3.3 ± 3.5 mg/L, P<.001). Both groups were similar in regards to BMI, infertility duration, and infertility diagnosis. However, the group that achieved pregnancy was significantly younger on average (25.5 ± 5.4 vs. 29.2 ± 5.4 years, P=.012), which was not adjusted for in the analysis (21). Another similar study compared the hs-CRP levels 2 and 8 days after IUI and found no difference between pregnant and non-pregnant patients, but this study was limited by its small sample size (n = 42), and only 8 patients became pregnant (22).

The relationship between the serum hs-CRP levels in assisted reproductive technology cycles and outcomes is similarly inconsistent. The hs-CRP levels steadily increase from the initiation of controlled ovarian hyperstimulation to the time of oocyte retrieval (23). In fact, several studies suggest that elevated hs-CRP levels, specifically on the day of oocyte retrieval and fresh embryo transfer, are found in patients who achieved pregnancy than those who did not (23–25). These findings may be due to the increased levels of cytokines in the preparation for implantation, resulting in elevated hs-CRP concentrations, as opposed to chronic inflammation at baseline (26). Yet other studies have suggested that there is no correlation between the IVF outcomes and hs-CRP levels (27, 28). The implications of these findings for IVF outcomes are unclear because the studies to date yield conflicting results.

A recent study of 100 infertile women who experienced a missed abortion after the IVF or OS-IUI compared the relationship between hs-CRP levels and euploid miscarriage. Chromosomal microarray testing was performed on products of conception retrieved after dilation and curettage and was performed in patients undergoing fertility treatment for diminished ovarian reserve, male factor infertility, tubal factor infertility, polycystic ovarian syndrome, and endometriosis. They found that patients with hs-CRP levels ≥0.75 mg/L were more likely to have a euploid miscarriage as opposed to an aneuploid loss (odds ratio [OR], 5.5; 95% CI, 1.2–25.2, P=.03) (29). The greater proportion of euploid loss in the group with high levels of hs-CRP suggests that other potential factors, such as immune-mediated or inflammatory factors, may contribute to early pregnancy loss. These findings also suggest that the contribution of inflammation to euploid miscarriages may be underestimated if cytogenetics is not performed.

The main strengths of this study include its large size, multicenter design, well-characterized participants, complete reporting of pregnancy outcomes, and the standardized timing of baseline hs-CRP concentration measurements. The primary limitation is that only a single hs-CRP value per patient was captured. There is evidence that a within-person variability of hs-CRP exists, particularly in those with higher levels; however, this finding is based on a study that included both men and women, without accounting for variations related to menstrual cycle timing in women (30). Although only a single hs-CRP level was collected in this study, the timing of collection was standardized to occur in the early follicular phase for all patients. Secondarily, the American Heart Association categories for hs-CRP were established for cardiovascular risk assessment using data that included men and women of all ages; it is possible that alternative cut-points would better reflect inflammatory markers for reproductive health. While differences in the pregnancy loss rate among hs-CRP groups were noted, our study was not adequately powered to detect a more modest difference in the live birth rate. Further studies are needed to confirm these findings and refine hs-CRP concentration cut-points for reproductive outcomes. Should these findings be confirmed, basal hs-CRP concentration may have the potential to serve as a clinical marker to identify patients at increased risk of pregnancy loss. If so, additional investigations of targeted interventions that reduce inflammation are needed to assess the effects on pregnancy outcomes.

CONCLUSION

We found that the risk of pregnancy loss was greater in women with unexplained infertility after OS-IUI when the hs-CRP level was higher. The risk, by baseline hs-CRP level as an indicator of inflammation, may be present with levels as low as >1 mg/L. The optimal cut-point to discriminate between normal and elevated hs-CRP concentrations from a reproductive standpoint remains unclear.

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