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Revisiting the progesterone to oocyte ratio

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Abstract

Objective—To critically evaluate the P to oocyte (O) ratio (P/O) in the prediction of live birth in assisted reproductive technology (ART) cycles.

Design—Retrospective cohort study.

Setting—Not applicable.

Patient(s)—A total of 7,608 fresh autologous ART ET cycles.

Intervention(s)—None.

Main Outcome Measure(s)—Live birth.

Result(s)—Generalized estimating equation (GEE) models and receiver operating characteristic curves assessed the ability of P, O, and the P/O ratio to predict live birth. In univariate GEE models, P, O, and P/O were each associated with live birth. However, in multivariate GEE models, the P/O ratio was not associated with live birth, but P alone was. This suggested that converting P and O into a ratio of P/O was not more helpful than the two independent variables themselves. Measures of overall model fit further suggested that P/O did not increase the predictive ability of the model over P and O alone. Receiver operating characteristic curves using incremental predictors further demonstrated that the P/O provided no incremental improvement in predicting live birth over P and O separately.

Conclusion(s)—These data suggest that P and O have utility in prediction modeling but demonstrate that additional oocytes were not protective from the negative association of P with

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live birth. There was no incremental improvement related to the P/O ratio specifically for predicting live birth over each variable independently.

Keywords

ART; premature progesterone elevation; progesterone; progesterone to oocyte ratio

Our understanding of the effect of prematurely elevated P on assisted reproductive technology (ART) outcomes has deepened dramatically in the past 6 years. In 2010, Bosch et al. (1) and Xu et al. (2) separately published data from more than 14,000 ART cycles demonstrating that premature P elevations were negatively associated with the likelihood of pregnancy. This negative association has been confirmed in a meta-analysis of more than 60,000 ART cycles from Venetis et al. (3). Further research has demonstrated that this negative association of P with pregnancy persists across various parameters of ART cycles to include GnRH antagonist cycles, GnRH and hCG trigger cycles, and in patients with young age, good-quality embryos, and blastocysts for transfer (4–7).

Recent studies have proposed that the relationship of P levels to treatment outcomes may vary by ovarian response and suggest the ratio of P to oocytes (P/ O) as an alternative and robust predictor of the likelihood of pregnancy. The body of literature demonstrating a relation of increasing P/O with decreasing pregnancies proposes the ratio to be a better predictor of pregnancy than P alone and recommends various thresholds for use of P/O (8–10). These assertions warrant further consideration. Among the questions raised by these studies, foremost is with regard to biologic plausibility. Elevated P is not associated with poor oocyte quality, donor–recipient outcomes, or subsequent frozen–thawed cycle outcomes (3). Further, the literature suggests elevated P causes premature advancement of the endometrium in fresh transfer cycles (3). Theoretically it should not matter how many follicles are producing the elevated P level, but rather what the level is. In other words, if sufficient P is produced to advance the endometrium, biologic plausibility suggests that endometrial advancement will occur whether that sufficient P was generated from a few or numerous follicles.

Second, the ratio P/O utilizes two variables independently associated with live birth and raises questions regarding the implications of use of ratios in statistical prediction models. Statistical considerations and potential issues with use of ratios have been described in the biomedical and statistical literature and suggest consideration of alternative approaches for modeling of variables comprising ratios (11, 12). Prior studies have suggested that P/O is superior to P alone, but it is unclear whether the P/O ratio per se provides optimal prediction, compared with alternative approaches for inclusion of O in models. Given that P and O are already demonstrated independent predictors of live birth, the approach for use of P and O to yield optimal predictive ability is not established. Our objective was to assess the ratio of P/O and other methods for inclusion of P and O for predictive probability for live birth.

We tested the hypothesis that the P/O adds incremental predictive probability over P and O as separate variables. The null hypothesis (that the P/O does not add incremental predictive probability) was based on the biologic plausibility that elevated P is likely to advance the

endometrium and decrease live birth, regardless of how many follicles generated that elevated P level.

MATERIALS AND METHODS

Study Design

This was a retrospective cohort analysis of fresh ART cycles from 2013–2015. Cycles were included if serum P was obtained on the day of trigger and a fresh embryo transfer occurred. The study was performed at Shady Grove Fertility Reproductive Science Center in Rockville, MD with institutional review board approval.

Patients

All patients who underwent a fresh autologous embryo transfer with known serum P levels measured on the day of trigger were included in the analysis. Exclusion criteria included cycles in which no embryo was transferred, donor oocyte recipients, frozen–thawed embryo transfers, and cycles without P measured on day of trigger.

Stimulation Protocol

Ovarian stimulation protocols included mixed FSH/hMG protocols with either GnRH agonist or GnRH antagonist for pituitary suppression. Oral contraceptive treatment was generally initiated 2 to 3 weeks before stimulation. For GnRH antagonist cycles, the antagonist was started when the lead follicle was 14 mm in size. For GnRH agonist cycles, 20 U of leuprolide acetate was administered SC during the last 3 days of oral contraceptive use. The leuprolide acetate was decreased to 5 U when ovarian suppression was confirmed with ultrasound and serum E_2 <5 pg/mL. Ovarian stimulation was achieved with both FSH and hMG preparations. When the lead follicle was ≥18 mm, 10,000 IU of hCG or 4 mg of GnRH agonist was used for final oocyte maturation. If GnRH agonist was used for trigger, 1,500 IU of hCG was administered after oocyte retrieval when <30 oocytes were obtained. In 2% of the study population, GnRH agonist trigger was used and ≥30 oocytes were obtained, in which case hCG was withheld after oocyte retrieval. In general, patients predicted to be higher responders were placed on an antagonist protocol and were more likely to receive GnRH agonist trigger. Serum P levels were obtained on the day of trigger. Oocyte retrieval was performed 36 hours after the trigger injection. Fertilization was achieved with either conventional IVF or intracytoplasmic sperm injection as clinically indicated. After retrieval, the majority of patients received vaginal P daily for luteal support. All patients received 2 mg estrace twice daily starting the evening of oocyte retrieval.

Ultrasound-guided ET was performed on day 3 or on day 5 if an adequate number of high-quality embryos were available. Embryos were graded as good, fair, or poor according to the simplified Society for Assisted Reproductive Technology scoring system (13). Serum hCG levels were assessed at 4 weeks' gestational age, followed by ultrasonography confirmation of a intrauterine pregnancy in all pregnant patients.

Serum P levels were measured using a solid-phase, competitive chemiluminescent enzyme immunoassay (Immunolyte 2000 Progesterone assay; Siemens Medical Solutions

Diagnostic). The lower limit of detection for the assay was 0.2 ng/mL, and the analytical sensitivity of the assay was 0.1 ng/mL. Intra-assay and interassay coefficients of variation were 6.7% and 7.2%, respectively.

Outcome

The primary outcome was live birth, defined as a live-born infant after the 23rd week of pregnancy.

Statistics

To evaluate approaches for inclusion of P and O in prediction models, values of P and O were used to create the P/O ratio. In addition, because the P/O ratio effectively utilizes 1 divided by oocytes (1/O) as a predictor, 1/O was evaluated as well. First, generalized estimating equation (GEE) models were utilized to assess relations of the probability of live birth with each of the independent variables in unadjusted and adjusted models, yielding odds ratio estimates. The GEE modeling was used to account for patients with multiple cycles and while allowing adjustment for covariates. Multivariable models were specified using variables significantly associated with live birth in univariate models ($P<.05$) and included the following: age, body mass index, total dose of gonadotropins, E_2 on the day of trigger, P on the day of trigger, oocytes retrieved, P/O, 1/ O, embryo stage, embryo quality, the number of embryos transferred, and the number of supernumerary embryos of high quality for vitrification. Interaction testing was used to determine whether the effect of P on live birth was similar as the number of oocytes retrieved increased. Progesterone and O were treated as continuous variables in the GEE models, to evaluate their effect across their entire range. As a measure of overall model fit, quasi-likelihood under independence model criteria (QIC) was also assessed with GEE models. Comparison of QIC values from different statistical models using the same study population can be used to indicate the best statistical model; lower values of the QIC reflect better model fit.

Second, receiver operating characteristic (ROC) curves were estimated to compare performance of a range of prediction models. The area under the curve (AUC) was used to reflect overall predictive ability, and models were evaluated for incremental predictive ability of P/O to predict live birth compared with P and O as independent predictors. Age was included in these models, owing to its strong association with the likelihood of live birth. Additional models evaluated included one, two, and three variables, to assess the predictive ability of adding P/O into the models.

To visually assess the relation of live birth with values of P and O, graphs were generated by grouping cycles with ≤3, 4–9, 10–14, and ≥15 oocytes and demonstrating live birth. These graphs were shown as both the actual rates of live birth (Fig. 1A) and the reduction in rate from the baseline live birth rate (Fig. 1B). Statistical analysis was performed using SPSS version 22 (IBM, Armonk, NY). A P value of <.05 was considered statistically significant.

RESULTS

A total of 7,608 fresh autologous ART ET cycles occurring in 6,157 subjects were included in the study. Baseline and stimulation characteristics of the study population are shown in

Supplemental Table 1 (available online). In all, 139 ART ET cycles were excluded owing to no P measured on the day of trigger. Of patients with a P value >2 ng/mL, 251 had all their embryos frozen, whereas 205 patients proceed with fresh embryo transfer. These groups were similar with regard to age, E_2 level, and oocytes retrieved. The median study patient age was 35 years (interquartile range [IQR], 32–39 years), median P on the day of trigger was 0.98 ng/mL (IQR, 0.70–1.30 ng/mL), and median oocytes retrieved were 12 (IQR, 8–17). Table 1 shows the unadjusted and adjusted odds ratio estimates with live birth. In univariate GEE analysis, age, embryo quality, embryo stage, P, O, and P/O were all significantly associated with live birth (Table 1). However, in multivariate analysis, P/O was not significantly associated with live birth, whereas P was independently associated (Table 1). This suggests that P/O did not add any predictive value incremental to that of P and O separately. When including age, embryo quality, and embryo stage in stepwise GEE models (data not shown), O was no longer statistically significant. This is likely because association of O with live birth is largely explained by age and the likelihood of having a good quality blastocyst for transfer.

The GEE model fit was assessed by comparing QIC for models that included either O or 1/O as a covariate and sequentially added P and then the P/O ratio. For models using O, inclusion of P/O resulted in a decrease of the QIC, suggesting P/O added a better model fit (Table 2). However, for models using 1/O, inclusion of P/O did not have a substantial impact on model fit. This result is consistent with previously described analyses and further suggests that the predictive ability of the P/O ratio is related to incorporation of 1/O rather than the P/O ratio per se.

Live birth decreased as P increased (odds ratio [OR] 0.87, P=.01) (Fig. 1A, Table 1). This finding persisted regardless of how many oocytes were obtained (Fig. 1B). Conversely, live birth increased as O increased (OR 1.03, P<.001) (Fig. 1A, Table 1). The number of oocytes retrieved was separated into the following groups: ≤3, 4–9, 10–14, and ≥15 oocytes. Each O group had a higher live birth rate than the group below it. However, within each group, live birth dropped as P increased (Fig. 1B). This suggests that having more oocytes was not protective from the negative association of P with live birth. Interaction testing of P with O on live birth was not significant (P=.44), further indicating that P had a negative association with live birth regardless of the number of O retrieved. In other words, no protective effect of increasing O was demonstrated.

Univariate ROC curves demonstrated that age had the highest predictive ability for live birth of all considered covariates (AUC = 0.61) (Table 3). The AUC was higher for O and 1/ O in predicting live birth (AUC = 0.58) than P (AUC = 0.53). In the two- and three-predictor models, P/O ratio added no incremental probability in detecting live birth compared with all other models (Table 3). A prediction model that included age, P, and 1/O had a slightly higher AUC (0.637) compared with models using age and P/O (AUC = 0.636) or age, P + O separately (AUC = 0.630). Inclusion of the P/O ratio as a covariate added no incremental predictive ability for live birth compared with using P and 1/O as separate variables.

DISCUSSION

These data support use of oocyte count and P in prediction models, because P, O, and P/O were all associated with the likelihood of live birth. However, the P/O ratio added no additional predictive value to the two variables separately, implying that the relation of P with live birth does not vary by the number of oocytes impacting levels of P. From a biologic standpoint, this could be argued to be intuitive. The putative mechanism for the negative association of P on live birth is the advancement of the endometrium, leading to embryo–endometrial asynchrony and decreased implantation (5). This is based on evidence that elevated P alters gene expression within the endometrium to change endometrial receptivity (14). The effect of elevated P on live birth is ameliorated in the subsequent frozen embryo transfer cycle (4) or in a donor–recipient transfer cycle (15). Additionally, elevated P is not associated with oocyte quality in autologous and donor cycles (1, 4, 5, 15). If the effect of elevated P on live birth occurs at the endometrium and not the oocyte, it can be argued that it should not matter whether that P comes from a few or many follicles.

The studies evaluating the P/O have suggested that higher number of follicles may be protective from the effect of elevated P, because it lowers the P/O (9, 10). This study clearly demonstrates that more follicles or oocytes were not protective from the negative association of P on live birth. Patients with a higher number of follicles are more likely to get pregnant, because they are younger, better responders, with increased embryos for selection; however, even good responders with many oocytes have decreased live birth rates as P increases (Fig. 1A and 1B). Importantly, it is clear from this dataset that a greater number of oocytes was not protective from the negative association of elevated P with live birth.

This study highlights several statistical issues that arise when using the ratio P/O as a covariate, which may provide insights to explain prior findings suggesting the P/O ratio to be clinically valuable. The P/O ratio incorporates two variables, both shown to each independently predict live birth (1, 2, 5, 16). Several studies have concluded that the P/O is superior to P alone (8, 9, 17); however, these studies failed to perform multivariate analyses to account for P and O as independent variables (8, 9, 17). Oocyte number is a strong predictor of live birth, and inclusion of O into the P/O would be expected to offer superior prediction to P alone. Our data support the utility of O as a predictor, but that the P/O ratio itself may not be the ideal approach to include O in statistical models. In fact, it is well established that inclusion of a ratio like P/O as a covariate in logistic models is a special case of including P and 1/O as separate predictors where the regression coefficient (i.e., the log odds ratio) is forced to take the same value for each, rather than allowing for different effects of each of P and 1/O. This has been demonstrated to negatively impact modeling in the instance of other ratio measures (12). One prior study performed multivariable regression analysis that included P/ follicle ratio plus oocyte number but did not consider alternative modeling approaches (10). Use of ROC curve analysis is one approach for evaluating incremental predictive ability of a biomarker when added to prediction models; our results show no incremental predictive ability of the P/O ratio itself for live birth beyond that of P and O as separate predictors.

We observed a stronger relation of 1/O with live birth compared with O, which may explain in part the predictive ability of P/O. Oocyte is not normally distributed, and the relationship between O and live birth is not linear. Rather, live birth increases sharply as O increases from a range of 1 to 10. As O continues to increase above 10, live birth rates also increase, but at a much less pronounced slope (Supplemental Fig. 1A). In other words, a patient with 15 oocytes may have a substantially higher probability of live birth than a patient with 5 oocytes, whereas a patient with 35 oocytes may have a relatively similar probability of live birth as a patient with 25 oocytes. Linear models of O and live birth under-exaggerate the relationship with O at low values and over-exaggerate the relationship at high O levels (Supplemental Fig. 1C). Conversely, 1/O creates a transformed O value that much more closely models the relationship of O with the log probability of live birth (Supplemental Fig. 1B and 1D). In univariate models, O and 1/O performed similarly. However, in all multivariate ROC models and in GEE modeling, 1/O performed slightly better than O.

It also must be noted that strength of effect should not be conflated with the magnitude of effect estimates, because they are completely dependent upon the scale of the variables being considered. An OR is the change in likelihood of the outcome (live birth) for the change in unit of predictor (O, P, or P/O). In the context of P, the OR indicates how much the likelihood of live birth decreases for every increase of 1 ng/mL of P. In this data set and others, the P/O has a larger magnitude OR estimate for predicting live birth than P alone (OR 0.03 vs. OR 0.87) as a result of the difference in scale between these two covariates. The ratio of P to O is distributed over a very small range, with a median of 0.08 (IQR, 0.06–0.12), whereas P has a larger range and a median of 0.94 (IQR, 0.67–1.27). The large OR for the P/O ratio in predicting pregnancy outcomes emphasized by prior literature is a simple algebraic artifact; a similar effect would occur modeling P in μg/mL instead of ng/mL. The effect of scale is emphasized by comparing O with 1/O. In GEE models, O had a wide range, from 1 to 68, and an OR of 1.03 (95% confldence interval 1.03–1.04). However, 1/O has a range that is mathematically confined from 0 to 1 and therefore a much larger magnitude of effect as reflected by an OR of 0.03 (95% confidence interval 0.01–0.06). Oocyte and 1/O represent the same information, but the data transformed into a ratio create a much more profound appearing OR.

In recent years it has become clear that the biologic underpinning of premature P elevation is not premature luteinization. This is supported by the clear association of P levels during ART stimulation with the dose of exogenous FSH and not that of LH, indicating the mechanism is not luteinization (1). In fact, exogenous LH may be helpful in converting the P substrate into androgens, which are then further aromatized into E_2. Observational data suggest that a higher LH/FSH ratio of ovarian stimulation medications decreases the risk of premature P elevation (18). Rather, the source of premature P elevation in GnRH analogue down-regulated cycles is an excess number of follicles, each contributing a small amount of P. The risk of premature P elevation is also associated with younger age, a larger follicular cohort, and GnRH antagonist cycles (1, 5). Taken together, these data demonstrate that the risk of P elevation is both intrinsic to patient factors and the result of controlled ovarian stimulation.

The strengths of this study include its large sample size, multivariate modeling, and incremental approach to predicting live birth. Although the data analysis is retrospective, the primary objective of the study was to assess for associations. Retrospective cohort studies are well suited for assessing associations when the appropriate confounding variables are available. Prior studies have used the P/follicle (P/F) ratio instead of P/O, because O may not reflect the entire pool of steroid producing follicles and is subject to potential variability based on the oocyte retrieval. On the other hand, follicle number may also have variability based on the quality and precision with which the ultrasound and documentation is performed. Given that this was a retrospective study and the data were not initially collected specifically to address this research hypothesis, we believed that oocytes represented a more consistent and objective data point than follicles. However, we did perform the same analyses detailed in this article for P/F and found similar results to our reported outcomes for P/O (data not shown).

In conclusion, these data do not demonstrate any incremental improvement in the P/O ratio for predicting live birth over each variable independently. The data further demonstrate that additional oocytes are not protective from the negative association of P with live birth. In addition to demonstrating the statistical underpinnings of the P/O ratio, these data are clinically relevant in demonstrating that even good-responder patients with many oocytes have a baseline reduction in live birth as P increased.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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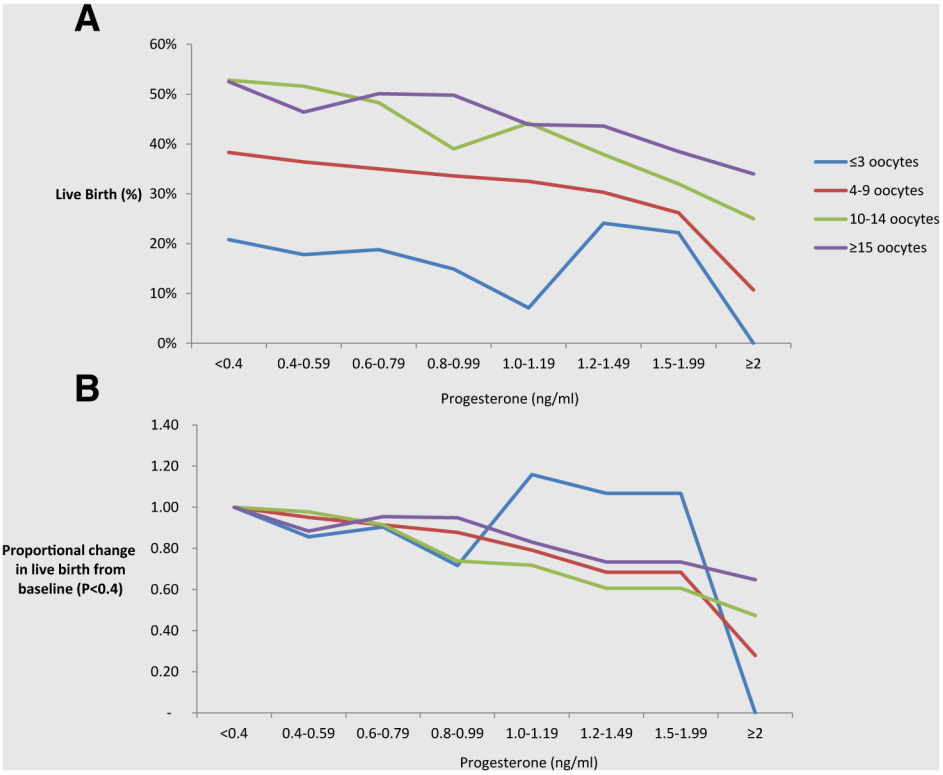

FIGURE 1.

(**A**) Live birth rate for patients with ≤3, 4–9, 10–14, and ≥15 oocytes by P levels. (**B**) Proportional chance in live birth from baseline (*P*<.4 ng/mL). The graph demonstrates that all oocytes groups had a similar reduction in live birth, regardless of the number of oocytes retrieved.

TABLE 1

Unadjusted and adjusted GEE models for associations with live birth.

Variable	Unadjusted OR (95%CI)	*P* value	Adjusted OR (95%CI)	*P* value
Age	0.91 (0.90–0.92)	<.001	0.93 (0.92–0.95)	<.001
Body mass index (kg/m^2)	0.99 (0.98–0.99)	.02	0.98 (0.97–0.99)	.04
Gonadotropins (IUs)	0.99 (0.99–0.99)	<.001	0.99 (0.99–0.99)	.004
P (ng/mL)	0.74 (0.67–0.82)	<.001	0.81 (0.66–0.98)	.04
Oocytes retrieved	1.03 (1.02–1.04)	<.001	0.99 (0.97–1.01)	.12
P/O	0.03 (0.01–0.07)	<.001	0.53 (0.11–2.56)	.43
E_2 (ng/ml)	1.00 (1.00–1.00)	<.001	1.00 (1.00–1.00)	.003
1/O	0.03 (0.01–0.6)	<.001	0.43 (0.09–1.96)	.43
Embryo grade	2.31 (1.97–2.70)	<.001	2.19 (1.86–2.19)	<.001
Blastocyst stage	3.23 (2.85–3.66)	<.001	2.73 (2.34–3.19)	<.001
No. of embryos transferred	0.69 (0.65–0.75)	<.001	1.12 (1.02–1.23)	.01
No. of supernumerary vitrified embryos	1.13 (1.11–1.16)	<.001	1.03 (1.01–1.06)	.02

Note: Adjusted models included all variables in the table (those found to have a $P<.05$ in univariate GEE models).

TABLE 2

Evaluating the contribution of P/O ratio incremental to P and O to models of live birth.

				Overall model fit (AIC)	
Approach for modeling O	**OR**	**95% CI**	**P value**	**QIC**	**QICu**
Count					
Model 1					
1. P	0.68	0.61–0.76	<.0001	5,952.33	5,952.31
2. O	1.03	1.02–1.04	<.0001		
Model 2					
1. P	0.96	0.84–1.09	.58	5,936.43	5,935.92
2. O	1.00	0.99–1.02	.26		
3. P/O	.02	0.01–0.08	<.0001		
1/count					
Model 1					
1. P	0.64	0.57–0.71	<.0001	5,935.07	5,935.00
2. 1/O	0.02	0.01–0.04	<.0001		
Model 2					
1. P	0.69	0.58–0.84	<.0001	5,935.12	5,935.51
2. 1/O	0.03	0.01–0.13	<.0001		
3. P/O	0.40	0.07–2.01	.28		

Note: Lower QIC values demonstrate an overall higher quality of model fitness. P/O did not improve model fit when 1/O was included in the model.

TABLE 3

Receiver operating characteristic curves evaluating 1, 2, and 3 predictor models for determining live birth.

Predictors	AUC
1 Predictor model	
Age	0.617
O	0.582
1/O	0.582
P	0.533
2 Predictor model	
Age	
1/O	0.628
Age	
O	0.623
Age	
P	0.622
P/O	0.597
3 Predictor model	
Age	
P	
1/O	0.637
Age	
P/O	0.636
Age	
P	
O	0.630

Note: P/O was considered a 2 predictor model, because it incorporates both P and 1/O into the model.