Prognostic value of a serum β-hCG cut off, 12 days after fresh embryo transfer, on predicting live birth among Ugandan women

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Abstract

Background: Human Chorionic Gonadotropin (hCG) is secreted by the embryo as early as the first week of life. Several studies have proven the potential of a single serum β hCG level, at 12 to 14 days after embryo transfer, to predict pregnancy outcomes after *In vitro* fertilization. However, these studies show significant heterogeneity, with paucity of data from African populations. This study aimed to evaluate the prognostic value of a serum β-hCG level cut off, 12 days after embryo transfer, on predicting livebirth among Ugandan women.

Methods: A Retrospective cross-sectional study. 337 fresh IVF cycles with serum β-hCG ≥5 mIU/mL, at 12 days after embryo transfer, were eligible. We abstracted participant characteristics, IVF cycle characteristics, livebirth, clinical pregnancy, and ongoing pregnancy data from each eligible cycle. We utilized the Youden index metric and the maximize_boot_metric method to link serum β-hCG levels to outcome data and determine the optimal cut off values.

Results: The optimal serum β-hCG cut off value for predicting livebirth was 437.42mIU/ml with a corresponding sensitivity and false positive rate of 72% and 31% respectively. The cut-offs for clinical and ongoing pregnancy, were 239.58 mIU/ml and 353.66 mIU/ml respectively. These corresponded with a sensitivity of 83% and 77% respectively, and a false positive rate of 27% and 33% respectively. The serum β-hCG cut off had a poor discriminatory performance for predicting live birth but moderate performance for predicting clinical and ongoing pregnancies.

Conclusion: A single serum β-hCG 12 days after cleavage embryo transfer has poor discriminatory performance in predicting live birth, albeit performing modestly in predicting clinical pregnancy and ongoing pregnancy among Uganda women.

Background

Although assisted reproductive technology (ART) has been available for over 4 decades, only 28% of oocyte retrievals result in live births across all age groups [1]. In addition, only 32.6% of embryo transfers result in live births [1]. In Europe, only 28% oocyte retrievals result in a pregnancy and 20.8% of oocyte retrievals result in a live birth [2]. Therefore, a proportion (29% [3]), of ART pregnancies end in early miscarriages with 58% of the losses happening by week 6 of gestation [3]. This proportion of pregnancy loss is high when compared to that from natural conception of intended pregnancies i.e., (13.5–22%) [4–9]. The ART seeking population is unique, with inherent risks for pregnancy loss such as advanced maternal [10], polycystic ovarian syndrome [11], sperm DNA (deoxyribonucleic acid) fragmentation [12] and obesity [13]. Considering the financial and psychosocial cost of ART, any outcome other than a live birth would not be desired. Maternal age, previous IVF (*In vitro* fertilization) attempts, number of good quality embryos, number of embryos transferred and blastocyst transfer are prognostic factors for live birth [14]. Others include Anti-Mullerian hormone (AMH) levels and antral follicle count (AFC) [15].

Several studies have investigated the utility of quantifying serum reproductive hormones such as human Chorionic gonadotrophin (hCG) [16], estradiol [17, 18] and progesterone [17] following 12–13 days embryo transfer. Except serum β-hCG, the rest of the hormones had limited value as biomarkers for live birth after ART[17]. HCG is a glycoprotein with a molecular weight of 40 kD. It consists of two non-covalently linked polypeptide subunits, α (93 amino acids) and β (145 amino acids). The α subunit of hCG shares structure homology to the α subunits of three other glycoprotein hormones i.e., luteinizing hormone (LH), Follicle stimulating hormone (FSH) and Thyroid stimulating hormone (TSH).The main source of hCG in pregnancy is the syncytiotrophoblast which differentiates from the trophoblast in the first week of embryonic life. This embryonic hCG maintains the life and steroidogenic activity of the corpus luteum. The corpus luteum secretes progesterone and estradiol that play vital roles in supporting embryo implantation. HCG also acts directly on uterine tissues to promote quiescence and immune modulation. The HCG levels in serum increase rapidly doubling every 36–48 hours from implantation and peak at 10 weeks of pregnancy. There after they plateau and decline by the end of the first trimester [Reviewed by 19].

E Confino, et al. [20], were the first to analyze the relationship between serum β-hCG levels after IVF and pregnancy outcomes. They successfully demonstrated that serial serum β-hCG after embryo transfer could predict gestational order, first trimester miscarriages and ectopic pregnancies. Several authors [17, 21–27] built on this work, demonstrating the ability of serial serum β-hCG levels to predict clinical and ongoing pregnancies after IVF. Furthermore, others [16, 28–35] have extensively evaluated the ability of a single serum β-hCG level, taken 12–16 days after embryo transfer, to predict pregnancy outcomes after IVF.

This wealth of literature on the utility of serum β-hCG is heterogenous in the type of measurement (serial versus single measurement), day of measurement (day 12 to 18), preceding IVF milestone (oocyte retrieval vs embryo transfer), reporting (sensitivity, specificity, predictive values, and area under the curve characteristics), definition of viability (> 12 weeks, > 20 weeks, clinical pregnancy, and live birth) and cycle characteristics (fresh versus frozen cycles and cleavage vs blastocyst transfers). Furthermore, these studies were done among American, European, and Asian populations with a paucity of data among African populations. As such, the utility of these cut offs maybe limited in our setting, considering that serum β-hCG raise in early pregnancy is race specific [36–39]. Therefore, this study aimed to evaluate the prognostic value of a serum β-hCG level cut off, 12 days after a fresh cleavage embryo transfer, on predicting livebirth among Ugandan women.

Method

Design

Retrospective cross-sectional study.

Setting

Life Sure Fertility and Gynaecology Centre is located in peri urban Kampala, in Uganda. It is a private specialized centre providing diagnostics and therapeutics in fertility and assisted reproduction. The catchment area of the clinic is heterogenous with patients coming from the city centre, peri urban area and rural areas of all over Uganda. The clinic is run by two reproductive medicine specialists ,three fertility nurses and two embryologists. The centre performs approximately 200 IVF cycles per year.

Study population

The medical records of patients who underwent a fresh IVF cycle and got pregnant (positive pregnancy test 12 days after embryo transfer), from January 2009 to December 2020, were retrieved.

Eligibility

All fresh cycles with serum β-hCG ≥ 5 mIU/mL at 12 days after embryo transfer were included in analysis. All heterotopic pregnancies, IVF cycles with incomplete or missing outcome data were excluded.

Laboratory

The serum β-hCG levels were measured by an automated quantitative enzyme linked fluorescent immunoassay (ELFA) (VIDAS®; bioMérieux; FRANCE) (see Additional file 1).

IVF Treatment protocol

The centre utilizes the long protocol, intensive luteal phase support and oral estrogen for endometrial priming in oocyte recipient cycle (see Additional file 2)

Outcomes

The primary outcome was to determine the discriminative ability of an optimal β-hCG cut off, 12 days after embryo transfer, in predicting a livebirth. Livebirth was defined as delivery of a live fetus at or after 28 weeks of gestation (this is based on National guidelines for the cut off of viability). The secondary outcomes included the discriminative ability of an optimal β-hCG cut off, 12 days after embryo transfer, to predict a clinical pregnancy and an ongoing pregnancy. Clinical pregnancy was defined as the presence of a gestational sac and yolk sac with a fetal node showing cardiac activity on ultrasonography performed between 8 and 9 weeks of gestation. Ongoing pregnancy was defined as a viable pregnancy at or beyond 20 weeks of gestation.

Sample size

The sample size for the diagnostic accuracy of a day 12 serum β-hCG cut off was based on the sensitivity and specificity of a day 14 serum β-hCG cut off reported by MA Eskandar, et al. [32]. Using the formula described by NM Buderer [40], the minimum sample size required was 199 IVF cycles. This assumed a target population livebirth prevalence of 33% and maximum acceptable 95% Confidence interval width of 10% (see Additional file 3).

Statistical analysis

Statistical analysis was performed using R statistical program [41]. The distribution of continuous variables was tested by the Shapiro-Wilks test. The student's t-test was used for continuous variables with a normal distribution whereas the Mann Whitney U test was used for variables with a skewed distribution. The Chi-square test was used for the comparison of proportions. The optimal cut off value was computed using the cutpointr package in R (https://CRAN.R-project.org/package=cutpointr) [42]. Cutpointr limits variability and overestimation inherent with other cut off tests. In addition, it performs robust out of sample estimates validation [42]. The Youden index metric was chosen to quantify the discriminatory ability and the maximize_boot_metric method, to select the optimal cut off value for serum β-hCG in predicting the outcomes. Subgroup analyses were done to estimate differences in cut offs by maternal age, source of oocytes (autologous or donor) and type of fertilization (IVF or ICSI). For P values, < 0.05 was considered significant.

Results

Population characteristics

The sample consisted of 337 IVF cycles. The mean age was 38.27±6.73 years, with the average duration of infertility at 6.54±4.58 years. Majority were primigravid (67%), with at least a tertiary level degree (71%), and slightly more than half with a professional occupation (56%). The common reasons for doing ART were the diagnosis of tubal blockage (67.4%) and or ovulatory dysfunction (60.8%), alone or in combination with another factor. All were fresh IVF cycles, with more than half of the women using donor oocytes (58.2%) and having conventional IVF (65.9%). All embryos transferred were at cleavage stage, and majority had four embryos transferred (72.1%) with grade IV (UK/NEQAS) the predominant morphological grade. The median serum beta hCG was 613.18 mIU/ml, with 80.1% of the pregnant women attaining at least a clinical pregnancy, 70.3% with a pregnancy beyond 20 weeks, and 65.9% with a live birth. Slightly over a third of the women had a pregnancy loss after the pregnancy test, with the main etiology being a missed abortion (51.3%). These population characteristics are summarized in Table 1.

Table 1

Population characteristics. N = 337; *; Each factor denominator is 337, **; using UK NEQAS embryo grading scheme.

Characteristic	Proportion (%), Mean±sd
Age (years; mean±SD)	38.27±6.73
Duration of infertility (years; mean±SD)	6.54±4.58
Parity	
0	67
1–2	24.9
3–4	5.9
> 4	2.1
Prior Miscarriage	
0	60.2
1–2	33.8
3–4	5
> 4	0.9
Education level	
No formal education	21.2
Primary	0.9
Secondary	6.9
Tertiary	71
Occupation	
None	23.7
Professional	56.1
Skilled	19
Unskilled	1.2
Indication for ART*	
Tubal factor	67.4
Ovulatory factor	60.8
Male factor	21.4
Unexplained infertility	12.5
Low ovarian reserve	2.7
Source of oocytes	
Autologous	41.8
Donor	58.2

Characteristic	Proportion (%), Mean±sd
Fertilisation method	
Conventional IVF	65.9
Intracytoplasmic sperm injection (ICSI)	34.1
Number of embryos transferred	
1	2.7
2–3	25.2
4	72.1
Embryo grade**	
4	94.1
3	4.2
2	1.5
1	0.3
Serum β-hCG (median; mIU/ml)	613.18
Clinical pregnancy	
Yes	80.1
No	19.9
Ongoing pregnancy	
Yes	70.3
No	29.7
Pregnancy loss	
Yes	34.1
No	65.9
Type of pregnancy loss (n = 115)	
Biochemical Pregnancy	33.0
Anembryonic	3.5
Ectopic pregnancy	5.2
Missed abortion	51.3
Spontaneous abortion	7
Livebirth	
Yes	65.9
No	34.1
Type of live birth (n = 222)	
Singleton	60.8

Characteristic	Proportion (%), Mean±sd
Twin	23.9
Triplet	13.5
Quadruplet	1.8

Optimal serum β-hCG cut-off values have a moderate to poor discriminatory ability for ART outcomes.

Using the Youden index metric, the optimal serum β-hCG cut-off value i.e., the value maximizing the Youden index, sensitivity, and specificity, was 437.42mIU/ml. Despite the high prevalence of livebirth in this population (65.9%), this cut-off value corresponds to a modest sensitivity (72%) and a high false positive rate i.e., $1 - specificity$, (31%), summarized in Table 2 and Fig. 3.

Table 2

Serum β-hCG optimal cut off values for each outcome and their associated metrics to quantify discriminatory ability. AUC; Area Under the curve, Se; sensitivity, Sp; specificity, ppv; positive predictive value, npv; negative predictive value, OR; odd ratio, RR; risk ratio and *; p value of a χ 2 -test on the confusion matrix.

Variable	Optimal cut off	AUC	Youden Index	Accuracy	Se	Sp	ppv	npv	OR	RR	p_chisquared*
Clinical pregnancy	239.58	0.85	0.56	0.81	0.83	0.73	0.93	0.52	13.23	3.09	< 0.01
Ongoing pregnancy	353.66	0.81	0.44	0.74	0.77	0.67	0.85	0.55	6.72	2.33	< 0.01
Livebirth	437.42	0.77	0.40	0.71	0.72	0.69	0.82	0.56	5.54	2.29	< 0.01

This cut-off was at variance with that for predicting clinical pregnancy and ongoing pregnancy, with the serum β-hCG value that maximized sensitivity (83% and 77% respectively) and minimized false positive rate (27% and 33% respectively), at 239.58 mIU/ml and 353.66 mIU/ml respectively. As shown in Table 2, these cut-offs are lower than that for predicting livebirth but carry comparable false positive rates (27–33%). Except for modestly predicting clinical pregnancy with a maximum Youden index of 0.56, serum β-hCG cut-off values had poor discriminatory performance for predicting ongoing pregnancy and livebirth. The respective Youden indices were 0.44 and 0.40, as summarized in Table 2, Fig. 1 and Fig. 2. Nonetheless, the out-of-bag estimates (shown in Table 3) for hCG-β cut-off values predicting all ART outcomes were normally distributed and nearly equivalent to the in-bag estimates.

Table 3

Summary statistics for Bootstrap optimal cut off values. Min; minimum, Max; Maximum, 5%; 5th percentile, 95%; 95th percentile, 1st Qu;1st Quartile, 3rd Qu; 3rd Quartile, SD; standard deviation of the mean.

Variable	Min	5%	1st Qu.	Median	Mean	3rd Qu.	95%	Max.	SD
Clinical pregnancy	87.06	146.46	187.59	233.92	249.52	296.80	399.58	611.72	82.26
Ongoing pregnancy	150.95	220.44	301.44	386.57	387.84	470.40	571.03	666.43	108.43
Livebirth	161.79	264.81	346.65	421.61	419.93	492.84	578.82	663.57	96.92

Maternal age has no association with serum β-hCG cut-off values for live birth

Although the optimal serum β-hCG cut-off values varied for all age groups (shown in Table 4 and Fig. 4), multivariate regression showed no effect on serum β-hCG levels (p = 0.756) and the Pearson's Chi-squared test showed no association with serum β-hCG cut-off values (p = 0.44). Nonetheless, the serum β-hCG cutoff value was lowest for the age category 36–40 and less than < 30 years respectively, at 301.76 and 387.39 mIU/ml respectively. These cutoff values achieved a

sensitivity of 82% and 73%, and a false positive rate of 39% and 25% respectively. Conversely, the serum β-hCG cutoff was highest for the 30–35 and > 40 years age categories, at 565.25 and 450.80 mIU/ml respectively. These cutoff values achieved a sensitivity of 65% and 73%, and false positive rate of 30% and 26% respectively. However, Youden index analysis indicated better performance for cut-off values in the < 30 and > 40 age categories, with lower false positive rates compared to other age categories (summarized in Table 4).

Table 4

Influence of maternal age on serum β-hCG optimal cut off values for livebirth. AUC; Area Under the curve, Se; sensitivity, Sp; specificity, ppv; positive predictive value, npv; negative predictive value, OR; odd ratio, RR; risk ratio and *; p value of a χ 2 -test on the confusion matrix.

Subgroup (years)	Optimal cut off	AUC	Youden Index	Accuracy	Se	Sp	ppv	npv	OR	RR	p_chisquared*
< 30	387.39	0.84	0.49	0.74	0.73	0.75	0.85	0.60	8.50	2.96	< 0.01
30–35	565.25	0.71	0.35	0.67	0.65	0.70	0.84	0.45	4.44	2.20	< 0.01
36–40	301.76	0.75	0.43	0.74	0.82	0.61	0.78	0.67	7.08	2.09	< 0.01
> 40	450.80	0.80	0.47	0.73	0.73	0.74	0.84	0.60	7.76	2.84	< 0.01

Oocyte source influences discriminatory performance of serum β-hCG cut-off value for live birth

At Youden index analysis, the optimal serum β-hCG cut-off predicting live birth was similar among women who used autologous and donor oocytes i.e 402.98 and 417.73mIU/ml respectively, as summarized in Table 5, and Fig. 5. Although equally suboptimal, the optimal serum β-hCG cut-off among women who used autologous oocytes yielded a better discriminatory performance (Youden index: 0.45) and false positive rate of 24% compared to women that used donor oocytes (Youden index: 0.34, false positive rate: 44%). Multivariate analysis showed that compared to donor oocytes, using autologous oocytes reduced serum β-hCG (p = 0.008).

Table 5

Influence of oocyte source on serum β-hCG optimal cut off values for livebirth. AUC; Area Under the curve, Se; sensitivity, Sp; specificity, ppv; positive predictive value, npv; negative predictive value, OR; odd ratio, RR; risk ratio and *; p value of a χ 2 -test on the confusion matrix.

Subgroup	Optimal cut off	AUC	Youden Index	Accuracy	Se	Sp	ppv	npv	OR	RR	p_chisquared*
Donor	417.73	0.75	0.34	0.71	0.78	0.56	0.79	0.55	4.57	1.78	< 0.01
Autologous	402.98	0.80	0.45	0.72	0.69	0.76	0.84	0.58	7.12	2.93	< 0.01

Table 6

Influence of fertilization method on serum β-hCG optimal cut off values for live birth. ISCI; intracytoplasmic sperm injection, IVF; *in vitro* fertilisation, AUC; Area Under the curve, Se; sensitivity, Sp; specificity, ppv; positive predictive value, npv; negative predictive value, OR; odd ratio, RR; risk ratio and *; p value of a χ 2 -test on the confusion matrix.

Subgroup	Optimal cut off	AUC	Youden Index	Accuracy	Se	Sp	ppv	npv	OR	RR	p_chisquared*
ICSI	509.81	0.78	0.44	0.68	0.62	0.82	0.68	0.47	7.40	3.42	< 0.01
IVF	402.5	0.78	0.42	0.73	0.80	0.62	0.73	0.65	6.58	2.12	< 0.01

Mode of fertilization has no effect on the discriminatory performance of serum β-hCG cut-off value.

Using the Youden index metric, the optimal serum β-hCG cut-off value that maximized performance metrics was 402.5 mIU/ml for pregnancies conceived following conventional *in vitro* insemination. This cut off corresponded to a sensitivity of 80% and a high false positive rate of 38%. This differed from pregnancies following ICSI, which has an optimal cut-off

of 509.81 mIU/ml, corresponding to lower sensitivity 62% but a lower false positive rate of 18%. Despite, the difference in false positive rate, Youden index metric indicated similar predictive performance for the cut off of among pregnancies after ICSI (0.44), and pregnancies after conventional *in vitro* semen insemination (0.42). Furthermore, multivariate analysis showed no effect of mode of fertilization on serum β-hCG levels (p = 0.139).

Discussion

Although a wealth of literature exists on the discriminatory ability of a single serum β-hCG value on predicting pregnancy outcomes after IVF, significant heterogeneity and lack of local population data limit its application in our setting. This study aimed to evaluate the prognostic value of a single serum β-hCG cut off, 12 days after embryo transfer, on predicting pregnancy outcomes among Ugandan women.

In this population, a single serum β-hCG value had limited discriminatory ability to predict pregnancies that would yield a live birth. The cut off of 437.42mIU/ml is within range to that reported by [43](495 mIU/ml), [44] (377.8mIU/ml), and [45] (386 mIU/ml). However, the reported sensitivity varied between a comparable 75.9% [44] and a higher 80% [43]. In addition, the false positive rate, indicated similar suboptimal performance, ranged between a lower 23.4 [43] and a comparable 38.8% [44]. But for the most part, our population cut off was 2–4 fold higher than that reported by others such as 50mIU/ml [46], 76mIU/ml [33], 78mIU/ml [47], 85mIU/ml [45], 131 mIU/ml [48]; 104.5mIU/ml [27], 145mIU/ml [29], 199 mIU/ml [49], 222.86 mIU/ml [50], 253 mIU/ml [49], and 315.65mIU/ml [32].The associated false positive rates indicated variable predictive performance and ranged between 10% [47] and 50% [49].

The higher cut off in this study probably resulted from high proportion of multiple embryo transfers (2–4 embryos making up 98%) and subsequent high rate of multiple pregnancies at delivery (39%). Multiple pregnancies confer higher cut offs of serum β-hCG compared to singletons [45]. In addition, significant heterogeneity in the interval between embryo transfer and serum β-hCG reading, could account for the variation between this study's cut off and that report by others. The interval varied by definition i.e, after oocyte retrieval [27, 44, 49] or after embryo transfer [43, 45, 48, 50, 51]. The interval also varied by duration i.e, 14–16 days after oocyte retrieval [27, 44, 47, 49] and 12–16 days after embryo transfer [43, 45, 48, 50–52]. Furthermore, majority of the studies used ROC (Receiver Operator Characteristic) analysis compared to our Youden index metric analysis to determined optimal cut offs. Importantly, these cut off values are not absolute and are to be interpreted with caution since, the lowest cut off, corresponding to the 5%centile, was 264.81 mIU/ml. This was echoed by Y Wu and H Liu [53], were optimal cut offs as low as 108.6 mIU/ml predicting live birth albeit with a false positive rate over > 50%.

The cut offs for clinical pregnancy and ongoing pregnancy had a modest performance with the Youden index metric with cut off values at 239.58 mIU/ml and 353.66 mIU/ml respectively. The cut off for clinical pregnancy was within range of that reported by others [50, 54]. In addition, cut off reported by N Singh, et al. [31] and MA Eskandar, et al. [32], for ongoing pregnancy were within range of our population. However, the cut off for clinical pregnancy was 2 fold higher than in other populations such as: 80.4 mIU/ml [27], 86.8mIU/ml [18], 100 mIU/ml [55], 123 mIU/ml [48], and 111mIU/ml [56] .Equally the cut off was approximately 2 fold higher that reported by others, 131mIU/ml [48], 137mIU/ml [57], for ongoing pregnancy. Others have reported higher cut off for ongoing pregnancy at 500mIU/ml [16] and 542.45 mIU/ml [54]. Furthermore, basing on the AUC (area under curve) characteristic and false positive rates, serum β-hCG cut offs performed better in predicting clinical pregnancy and ongoing pregnancy compared to livebirth, as reported by others [27, 48, 50]

Serum β-hCG had better discriminatory performance in women less than 30 years or greater than 40 years of age. This can be explained by the similar age of utilized oocytes since women above 40 years are likely to have utilized donor oocytes and oocyte donors are usually less than 30 years of age. The lack of association between age and serum β-hCG cut off values is in variance with that reported [51, 56], and could have resulted from the small sample size and high proportion of donor oocyte utilization in this population. Serum β-hCG had better discriminatory performance among cycles that utilized

autologous oocytes compared to oocyte donor cycles. This probably because cycles using autologous oocytes had relatively more homogeneity in cycle characteristics compared to those using donor oocytes.

This study reports limited correlation with existing and studies and contributes to the ever-increasing variation in serum β-hCG cut off among different ART populations. Heterogeneity in population characteristics contributed to the disparity in cut off values between this study and others. Some of key characteristics that may have impacted the serum β-hCG cut off include: proportion of multiple gestations [45], embryo grade [56, 58], embryo developmental stage [47], fresh versus frozen embryo transfers [50, 56], maternal age [51, 56], and the interval between embryo transfer and serum β-hCG reading.

Conclusion

Although this population presents higher serum β-hCG cut off values for livebirth and other pregnancy outcomes, significant heterogeneity exists within the published literature. Furthermore, a single serum β-hCG 12 days after cleavage embryo transfer has poor discriminatory performance in predicting live birth, albeit performing better in predicting clinical pregnancy and ongoing pregnancy among Uganda women.

Abbreviations

AFC - Antral follicle count.

AMH - Anti-Mullerian hormone.

ART- Assisted Reproductive Technology.

FSH - Follicle stimulating hormone.

HCG- human chorionic gonadotrophin.

ICSI – Intracytoplasmic sperm injection.

IVF – *In vitro* Fertilization.

LH - Luteinizing hormone.

TSH - Thyroid stimulating hormone.

Declarations

Ethics approval

This study was approved by the St Francis Hospital Nsambya Research and ethics committee (REC).

Consent for publication

Not applicable

Availability of data and materials

The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.

Competing interests

The authors declare that they have no competing interests

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The authors received no specific funding for this work.

Authors' contributions

DZ developed the study design, performed data quality control, data analysis and wrote the manuscript. MWL developed the data analysis plan, preformed data quality control, and analysed the data. AK reviewed the study design, supervised treatment chart abstraction, conducted data analysis and revised the manuscript before submission. All authors read and approved the final manuscript.

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Figures

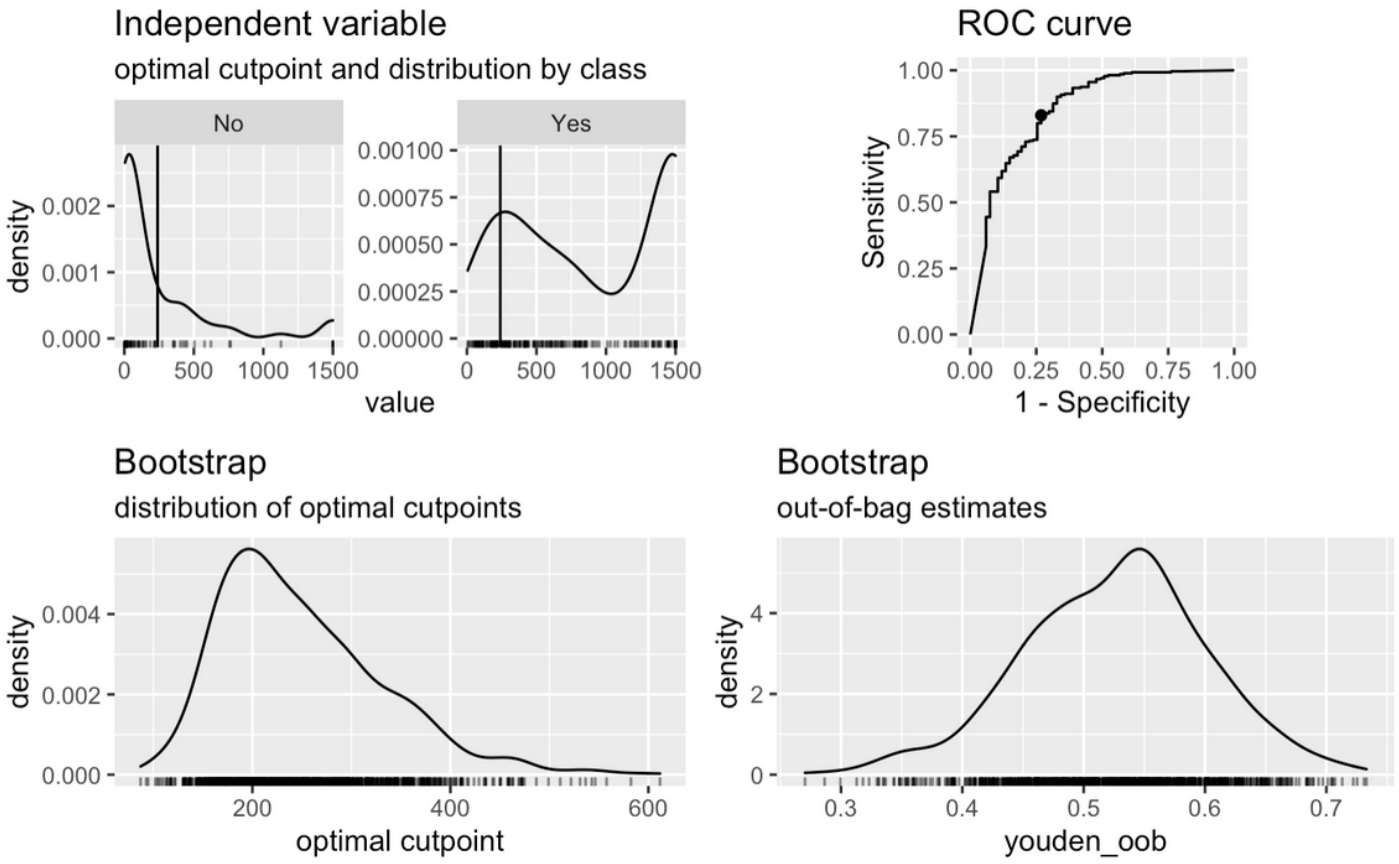

Figure 1

Serum β-hCG cut off performance when predicting clinical pregnancy. The top left showing the distribution of the predictor values per class, the top right showing the ROC curve, the bottom left showing the bootstrapped cutpoint (cut off) variability, and the bottom right showing the distribution of the out-of-bag Youden Index values.

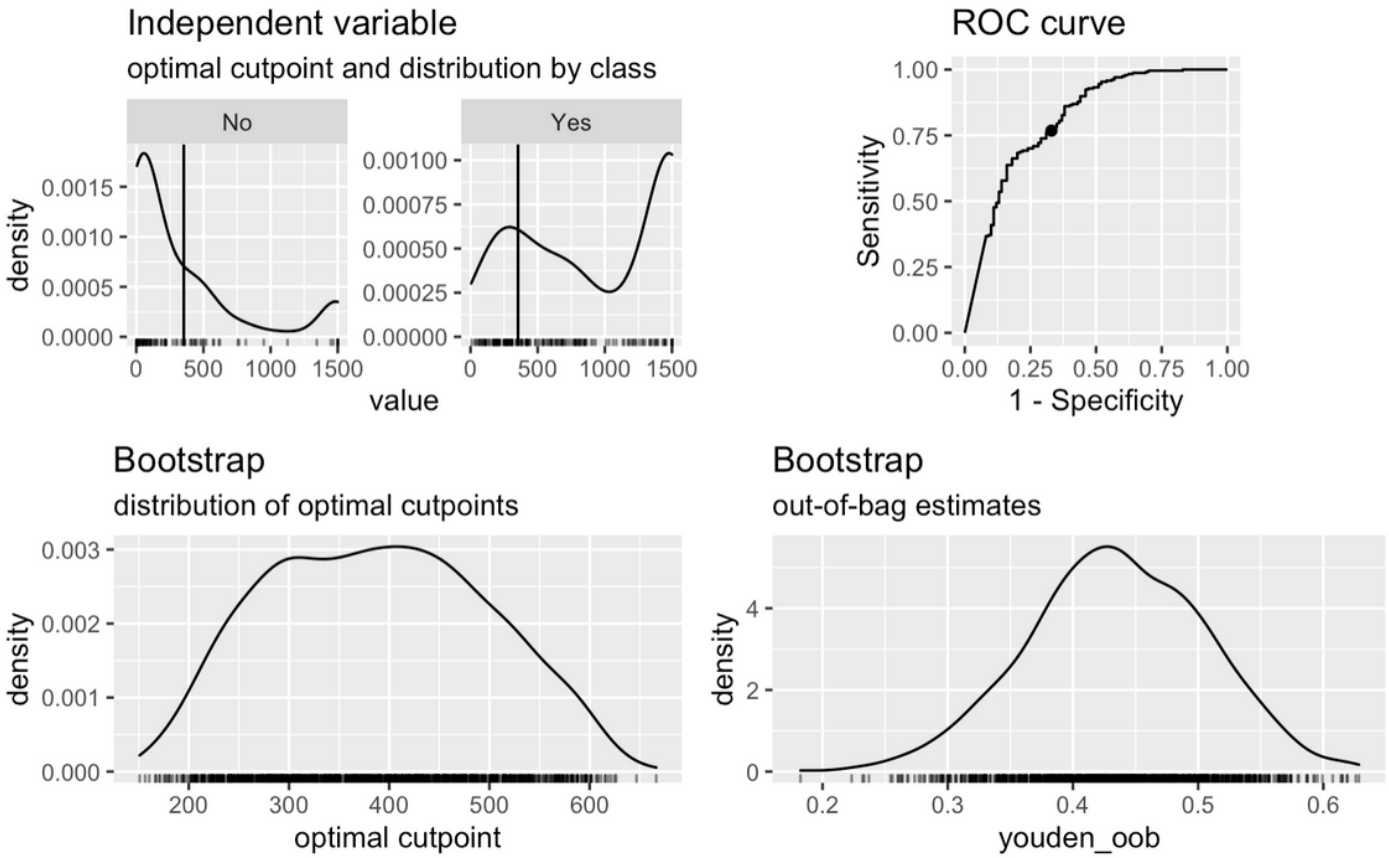

Figure 2

***Serum β-hCG* cut off performance when predicting ongoing pregnancy.** The top left showing the distribution of the predictor values per class, the top right showing the ROC curve, the bottom left showing the bootstrapped cutpoint (cut off) variability, and the bottom right showing the distribution of the out-of-bag Youden Index values.

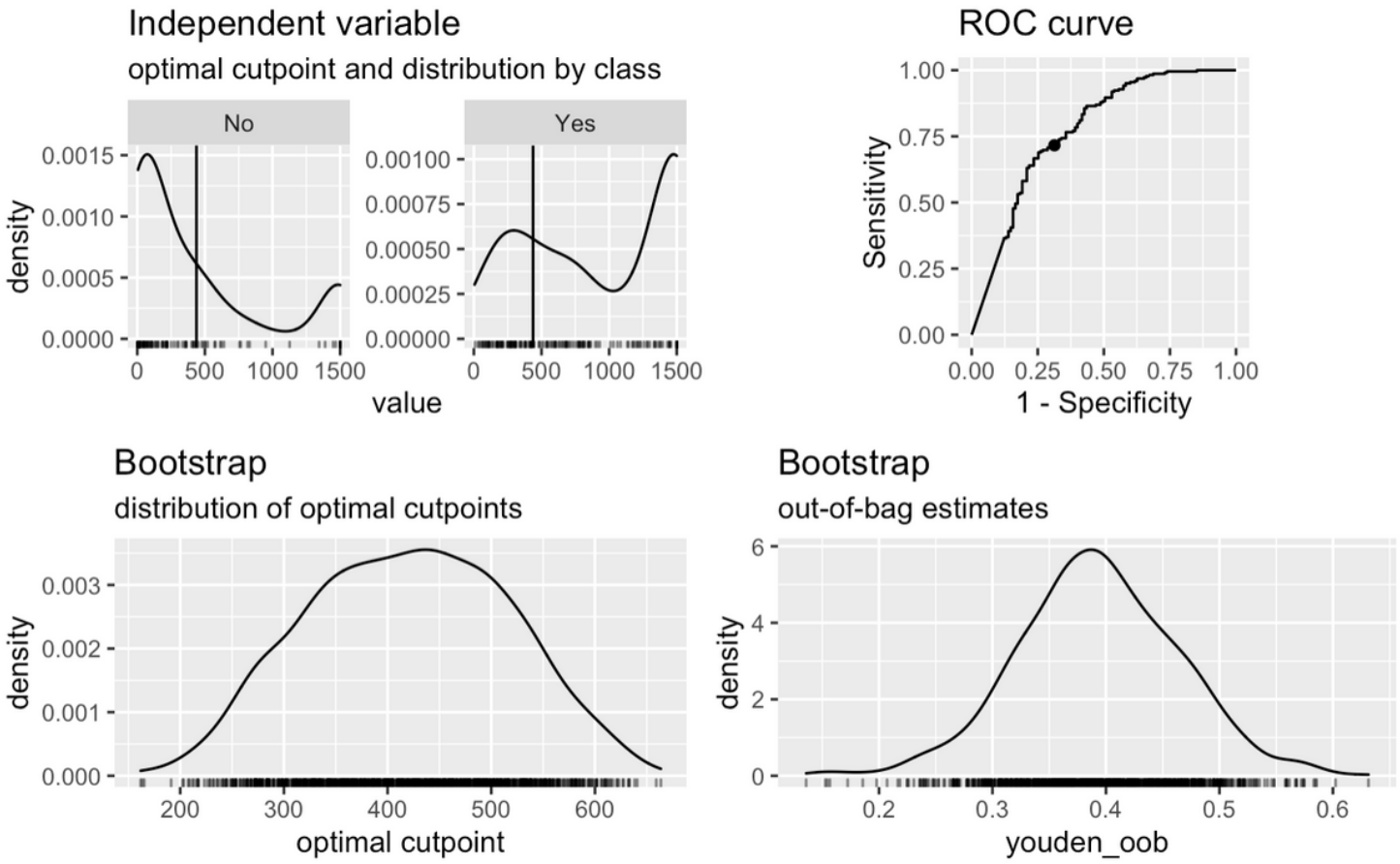

Figure 3

Serum β-hCG cut off performance when predicting livebirth. The top left showing the distribution of the predictor values per class, the top right showing the ROC curve, the bottom left showing the bootstrapped cutpoint (cut off) variability, and the bottom right showing the distribution of the out-of-bag Youden Index values.

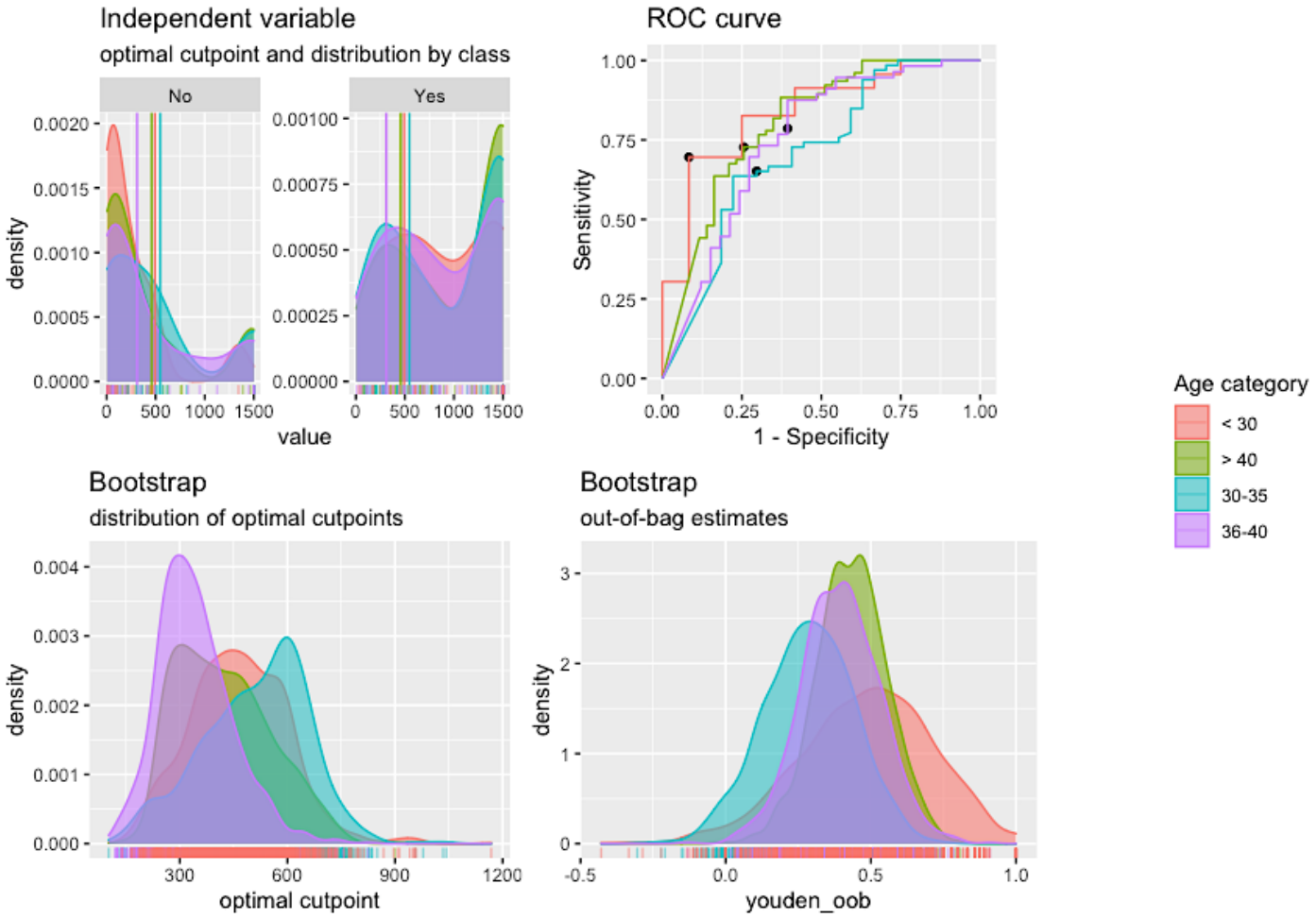

Figure 4

Influence of maternal age on Serum β-hCG cut off performance when predicting livebirth. The top left showing the distribution of the predictor values per class, the top right showing the ROC curve, the bottom left showing the bootstrapped cutpoint (cut off) variability, and the bottom right showing the distribution of the out-of-bag Youden Index values.

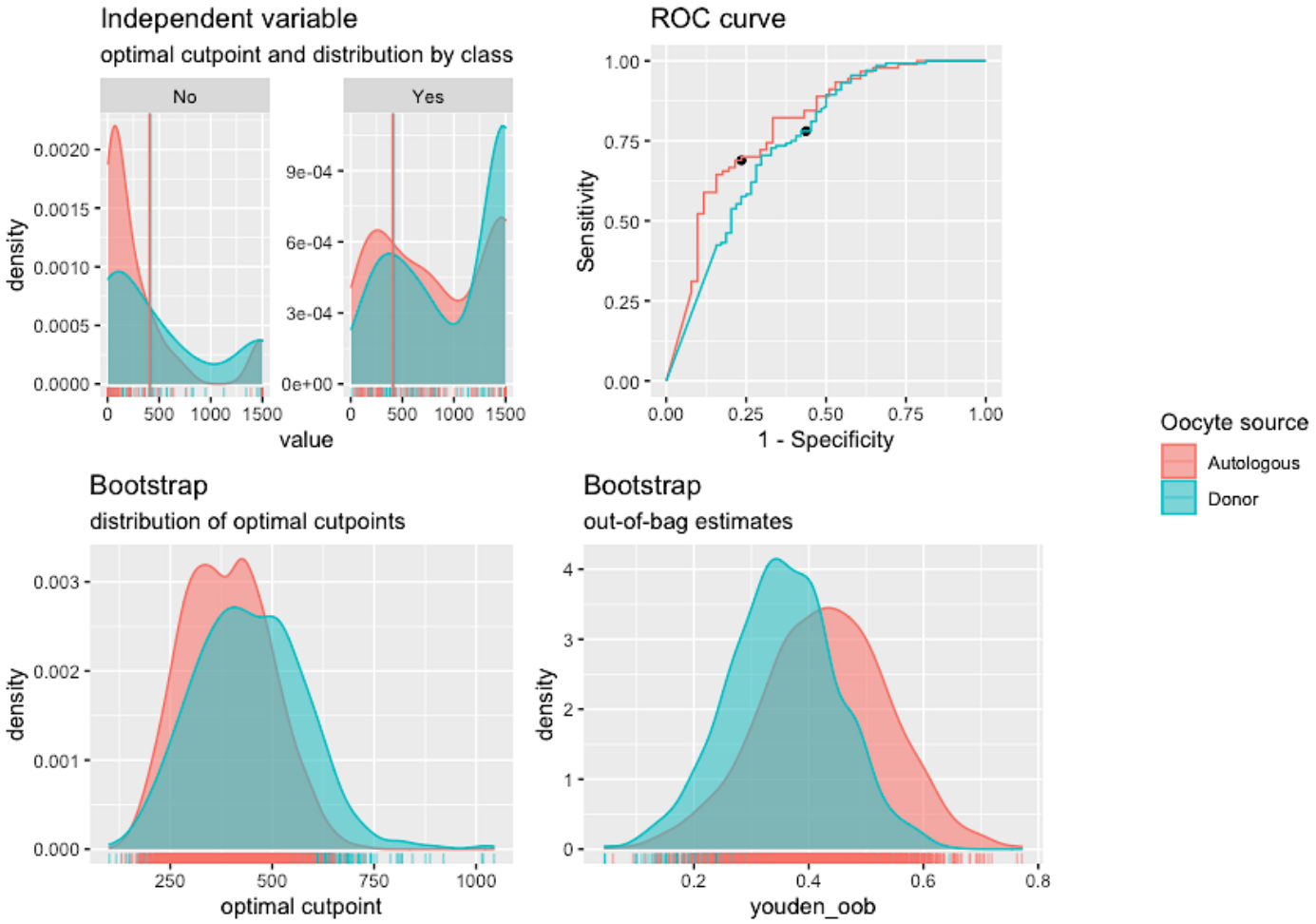

Figure 5

Influence of oocyte source on Serum β-hCG cut off performance when predicting livebirth. The top left showing the distribution of the predictor values per class, the top right showing the ROC curve, the bottom left showing the bootstrapped cutpoint (cut off) variability, and the bottom right showing the distribution of the out-of-bag Youden Index values.

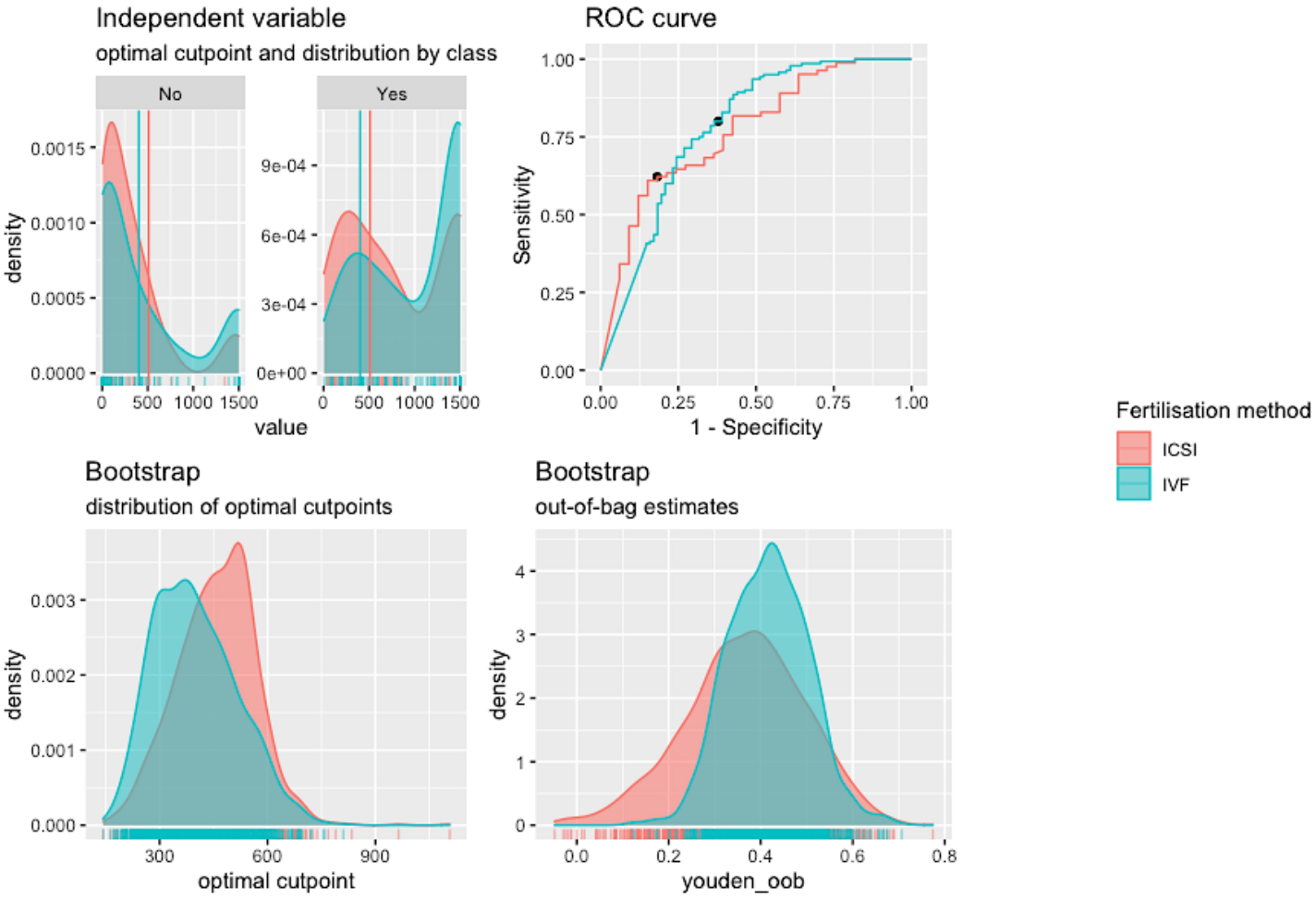

Figure 6

Influence of fertilisation method on Serum β-hCG cut off performance when predicting livebirth. The top left showing the distribution of the predictor values per class, the top right showing the ROC curve, the bottom left showing the bootstrapped cutpoint (cut off) variability, and the bottom right showing the distribution of the out-of-bag Youden Index values.

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