

Ranking embryos for transfer using a prediction model

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Introduction

Goal of embryo selection:

- To determine the number of embryos to transfer
 - maximize pregnancy chances, minimize multiple pregnancy chances
 - transferring only one embryo if there is a high chance of implantation
- To minimize the time to pregnancy
 - transferring the embryo with the highest implantation potential as early as possible
- Not to increase pregnancy chances

Mastenbroek et al., HR (2011)

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Introduction

- Morphological selection of embryos is the core of daily laboratory practise in IVF/ICSI.
- Morphological ranking and selection of embryos is based primarily on clinical experience and local protocols
- Previous prediction models: small cohorts, no external validation
- Evidence-based ranking strategy for embryos on day 3 is lacking



Aim

Prediction model that ranks embryos
in any given cycle according to
their implantation potential

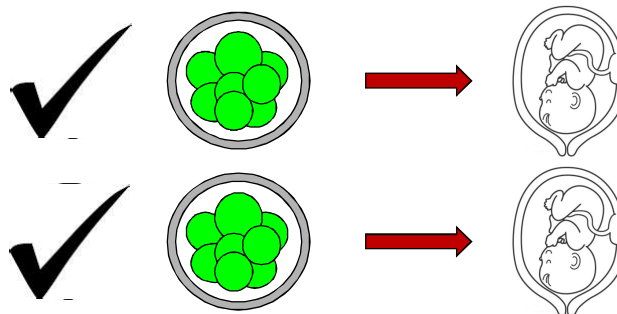


Methods

- All IVF/ICSI cycles between Jan 2004 and Sept 2011
- Center for Reproductive Medicine, Amsterdam, the Netherlands
- Development set: January 2004 and July 2009
- Validation set: August 2009 and September 2011

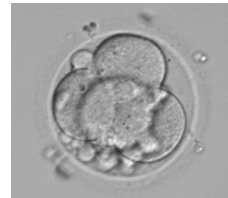
Methods

- Outcome: ongoing implantation
- Only cycles with exact traceability of embryos



Scoring embryo predictors

- Pronuclear scoring
- Early cleavage
 - Number of blastomeres on day 2 and 3
- Morphological score on day 2 and 3
 - Score 1: no fragmentation
 - Score 2: <20% fragmentation
 - Score 3: 20-50% fragmentation
 - Score 4: > 50% fragmentation
 - Non-uniform blastomere size: score was augmented with 1
- On day 3 compaction: morula
 - Score 1: full compaction
 - Score 2: 50 -<100% compaction
 - Score 3: < 50% compaction



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Puissant et al., Hum Reprod, 1987

Analysis

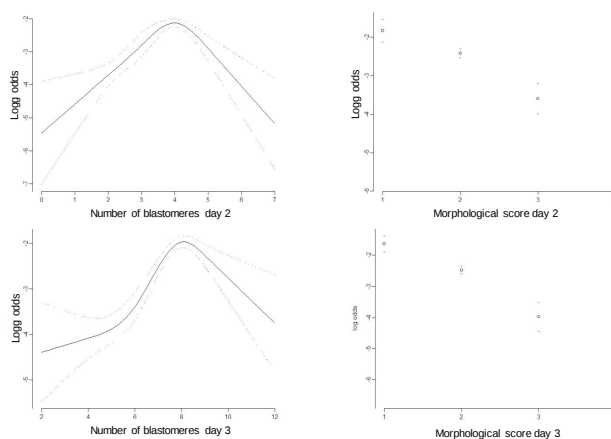
- Missing values completed by multiple imputation
- Continuous variables checked for linearity
- Logistic regression analysis:
 - Univariable ($p < 0.3$)
 - Multivariable (generalized likelihood ratio test statistics)
- Performance:
 - Discriminative capacity (AUC/c-statistic)
 - Calibration
- External, temporal validation

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Results – baseline data

	Development set		Validation set	
Age (SD)	35.6	(4.5)	35.8	(4.5)
Indication for IVF/ICSI				
Tubal pathology	538	20%	154	10%
Unexplained subfertility	739	28%	453	31%
Male subfertility	1168	44%	707	48%
Endometriosis	86	3%	55	4%
Oocyte donation	24	1%	4	0%
Others	336	13%	155	11%
Number of SET	605		550	
Number of DET	1793		683	
Number of TET	279		234	
Singletons	120		105	
Twins	127		47	
Triplets	0		0	

Results – Continuous variables



Results – Univariable analysis

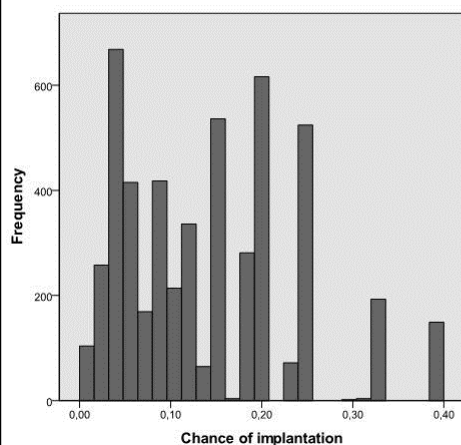
	β	OR	95% CI	P-value
Pronuclear score				0.26
2 PN (reference)				
1 PN	-1.25	0.28	(0.07-1.17)	0.08
0 PN	-0.18	0.84	(0.55-1.28)	0.41
Unknown	-1.15	0.32	(0.04-2.32)	0.26
2-blastomeres	0.48	1.61	(0.37-7.07)	0.53
Early cleavage	0.65	1.92	(1.42-2.59)	0.00
Number of blastomeres day 2	0.24	1.28	(1.15-1.41)	0.00
Number of blastomeres day 3	0.32	1.37	(1.28-1.47)	0.00
Morulae	0.32	1.37	(0.84-2.23)	0.20
Morphological score day 2	-0.83	0.04	(0.35-0.54)	0.00
Morphological score day 3*	-1.05	0.35	(0.28-0.43)	0.00
Progression from 4 blastomeres on day 2 to 8 blastomeres on day 3	1.28	3.59	(2.89-4.45)	0.00

Results – Multivariable analysis

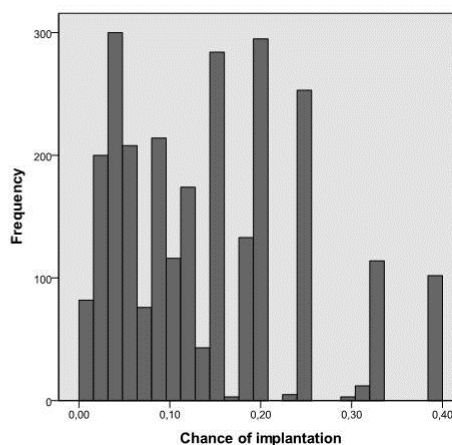
- Early cleavage
 - Yes / no
- Number of blastomeres on day 2
 - Number of blastomeres deviating from 4
- Number of blastomeres on day 3
 - Number of blastomeres deviating from 8
- Morphological score day 3
 - 1,2,3 or 4
- Morula on day 3
 - Yes / no

Calculated probabilities

a. Development set



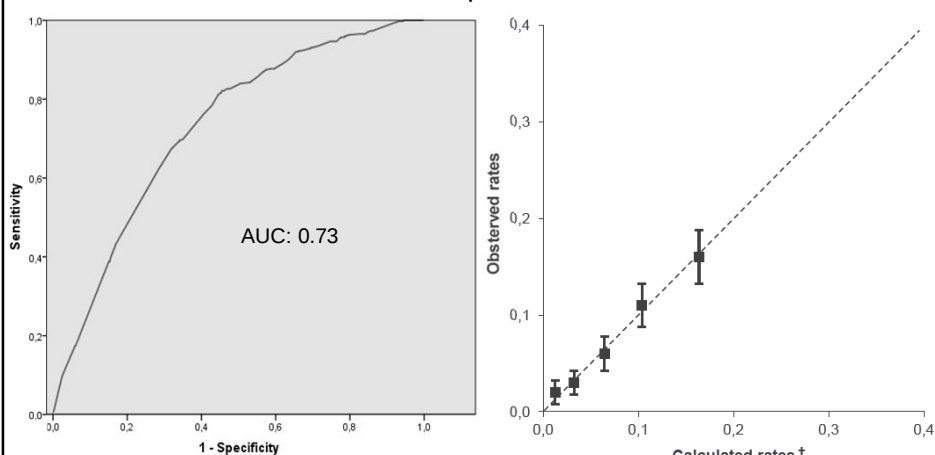
b. Validation set



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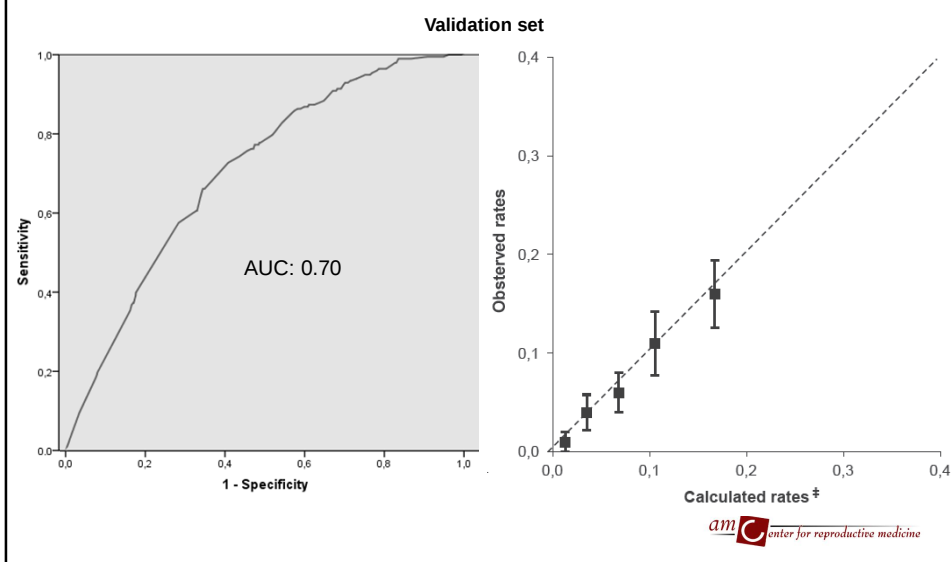
Results – ROC & Calibration

Development set



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Results – ROC & Calibration



Ranking embryos

	Early cleavage	Number of blastomeres day 2	Number of blastomeres day 3	Morphological score day 3	Morula on day 3	Total score
Embryo 1	no	2	3	3	no	67
Embryo 2	no	3	5	3	no	76
Embryo 3	no	4	12	2	no	81
Embryo 4	no	5	7	2	no	87
Embryo 5	no	3	NA	NA	yes	89
Embryo 6	yes	4	9	2	no	92
Embryo 7	no	4	8	2	no	93
Embryo 8	yes	4	NA	NA	yes	94
Embryo 9	no	4	8	1	no	98
Embryo 10	yes	4	8	1	no	100

Conclusion

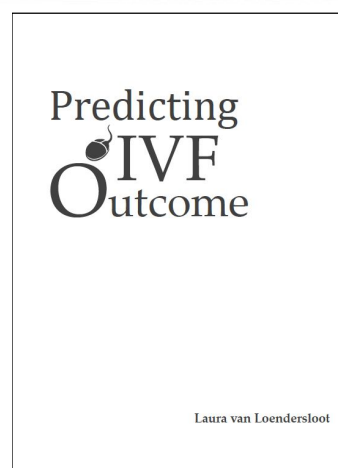
The model

- clearly distinguishes between embryos with high-, moderate- or low ongoing implantation potential
- it can help to create a more uniform embryo selection strategy for all laboratories transferring embryos on day 3 after oocyte retrieval.
- can be used by embryologists as an objective tool to rank embryos according to their implantation potential thereby aiding the selection of embryos for transfer.



Acknowledgements

- Madelon van Wely
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- Sjoerd Repping



van Loendersloot, et al., RBMO (2014, accepted)

Questions



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Is selection the way forward?

- History embryo selection
 - Low success → multiple embryos
 - Increased success → fewer embryos
- Selection necessary
 - reduced success after cryopreservation
- Recent developments challenge this concept
 - Improved cryopreservation
 - Endometrial receptivity affected by hyperstimulation
 - In natural cycles increased endometrial quality
 - Could counterbalance negative effect of cryopreservation

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Mastenbroek, et al., HR (2011)

Is selection the way forward?

- Cycles with disengagement of transfer
 - egg donation / OHSS
 - comparable / increased pregnancy rates
 - using slow freezing protocols (Paulson 1990; Check 1999; Shapiro 2008)
- Even better with vitrification
 - Higher pregnancy rates after vitrification in comparison with slow freezing (Abdelhafez 2010)
- First RCTs promising
 - Higher pregnancy rates after IVF without fresh transfer compared to IVF with fresh transfer
 - High responders (Aflatoonian 2010)
 - Normal and high responders, different protocol (Shapiro 2011)



Mastenbroek et al., HR (2011)

Is selection the way forward?

- Future...
 - Cryopreservation of all embryos
 - No fresh transfer
 - Transfer in subsequent natural cycles
- Selection methods
 - Will not improve overall pregnancy rates
 - If not 100% accurate → decrease pregnancy rates
 - » Holds for all current selection techniques
 - Might improve time to pregnancy
 - Earlier transfer of best embryos



Mastenbroek et al., HR (2011)