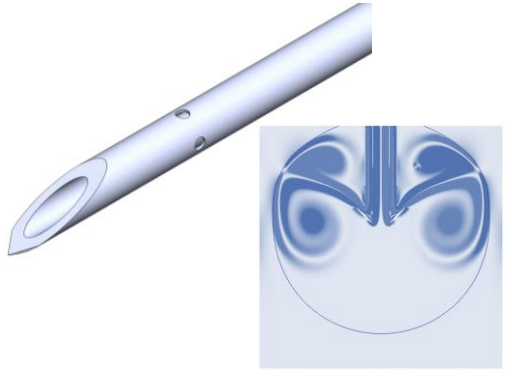
PSI Webinar: Drug Development in Women's Health

15 May 2024

A new flow-based design for double-lumen needles in IVF

Dr. Radu Cimpeanu
Warwick Mathematics Institute



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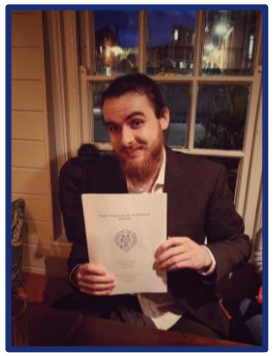
The research group and our work


Dr. Michael Negus (2022)


Dr. Ben Fudge (2023)


Oscar Holroyd (2025)


Sebastian Dooley (2026)


Minerva Schuler (2027)

Some activities in the wider collaborative group:

Drop dynamics

- Bouncing
- Coalescence
- Splashing
- Fluid-structure interaction


Liquid films

- Multi-physics modelling
- Asymptotic analysis
- Control theory
- Equation discovery


Industrial mathematics

Sustainable software

Outreach and art

Acknowledgements:

- **EPSRC** (CDT activities, EP/V051385/1 on liquid film control, EP/W032201/1 on ReproHacks) **and NSF** (EP/W016036/1)
- **UK Fluids Network** (Drop Dynamics and Interfacial Flows SIGs)

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UK FLUIDS NETWORK

@rcimpeanu

GitHub rcsc-group

The OxIVF needle team (2018-)

Hector Georgiou
Reproductive Medicine
Subspecialist Consultant

Radu Cimpeanu
Associate Professor (Reader) in
Applied Mathematics

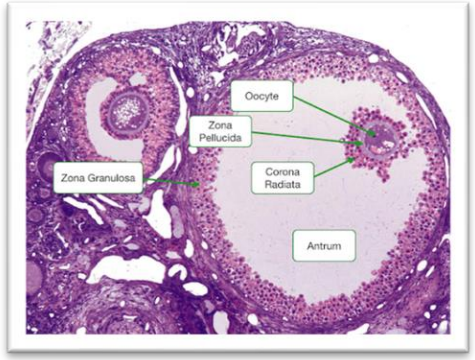
Alfonso Castrejón-Pita
Professor in
Engineering (Fluid Mechanics)

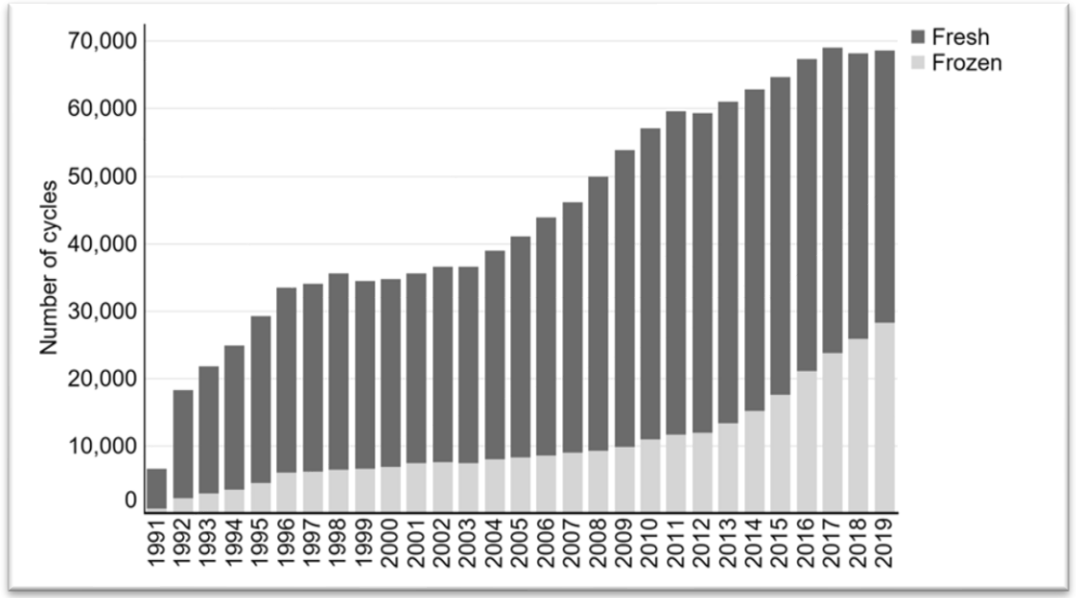
Lee Lim
Reproductive Medicine
Subspecialist Consultant

Manu Vatish
Professor of Obstetrics,
Bill & Melinda Gates Foundation Deputy Director
(Drug and Clinical Development)

The clinical problem

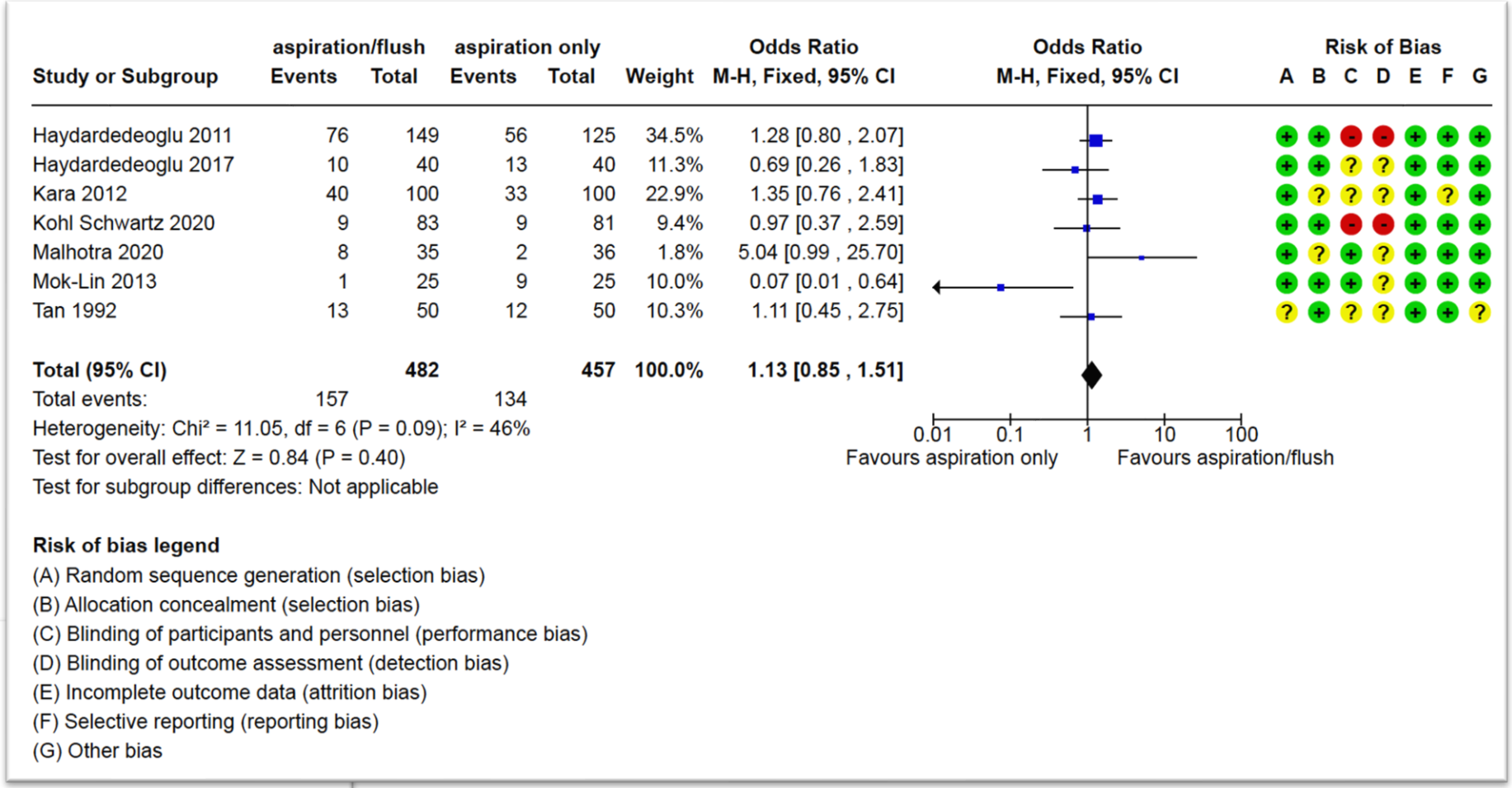
- 10% of couples suffer with infertility[1]
- IVF rates continue to increase in the UK[2], Europe[3], Australia[4] and the World[5]
- IVF success rate is low (32%)[6]
- IVF success is linked to the number of oocytes retrieved[7]
- Follicular flushing as a solution?





1. World Health Organization. Infertility is a global public health issue. https://www.who.int/reproductivehealth/topics/infertility/perspective/en/
2. Human Fertilisation & Embryology Authority. Fertility treatment 2014-2016. Trends and figures. https://www.hfea.gov.uk/media/2563/hfea-fertility-trends-and-figures-2017-v2.pdf
3. De Geyter C et al; European IVF-monitoring Consortium (EIM) for the European Society of Human Reproduction and Embryology (ESHRE). ART in Europe, 2014: results generated from European registries by ESHRE: The European IVF-monitoring Consortium (EIM) for the European Society of Human Reproduction and Embryology (ESHRE). Hum Reprod.2018 Sep 1;33(9):1586-1601. doi: 10.1093/humrep/dey242.
4.https://npesu.unsw.edu.au/sites/default/files/npesu/data_collection/Assisted%20Reproductive%20Technology%20in%20Australia%20and%20New%20Zealand%202019.pdf
5. ICMART World Report 2016
6. https://www.hfea.gov.uk/about-us/publications/research-and-data/fertility-treatment-2019-trends-and-figures/#Section1
7. Sunkara SK, Rittenberg V, Raine-Fenning N, Bhattacharya S, Zamora J, Coomarasamy A. Association between the number of eggs and live birth in IVF treatment: an analysis of 400 135 treatment cycles. Hum Reprod. 2011 Jul;26(7):1768-74. doi: 10.1093/humrep/der106. Epub 2011 May 10. PMID: 21558332.
Follicle image source: http://medcell.med.yale.edu/histology/ovary_follicle.php

IVF and follicular flushing



Study or Subgroup	aspiration/flush Events	Total	aspiration only Events	Total	Weight	Odds Ratio M-H, Fixed, 95% CI
Haydardedeoglu 2011	76	149	56	125	34.5%	1.28 [0.80 , 2.07]
Haydardedeoglu 2017	10	40	13	40	11.3%	0.69 [0.26 , 1.83]
Kara 2012	40	100	33	100	22.9%	1.35 [0.76 , 2.41]
Kohl Schwartz 2020	9	83	9	81	9.4%	0.97 [0.37 , 2.59]
Malhotra 2020	8	35	2	36	1.8%	5.04 [0.99 , 25.70]
Mok-Lin 2013	1	25	9	25	10.0%	0.07 [0.01 , 0.64]
Tan 1992	13	50	12	50	10.3%	1.11 [0.45 , 2.75]
Total (95% CI)		**482**		**457**	**100.0%**	**1.13 [0.85 , 1.51]**
Total events:	157		134			

Heterogeneity: Chi² = 11.05, df = 6 (P = 0.09); I² = 46%
Test for overall effect: Z = 0.84 (P = 0.40)
Test for subgroup differences: Not applicable

Risk of bias legend

(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias)
(D) Blinding of outcome assessment (detection bias)
(E) Incomplete outcome data (attrition bias)
(F) Selective reporting (reporting bias)
(G) Other bias

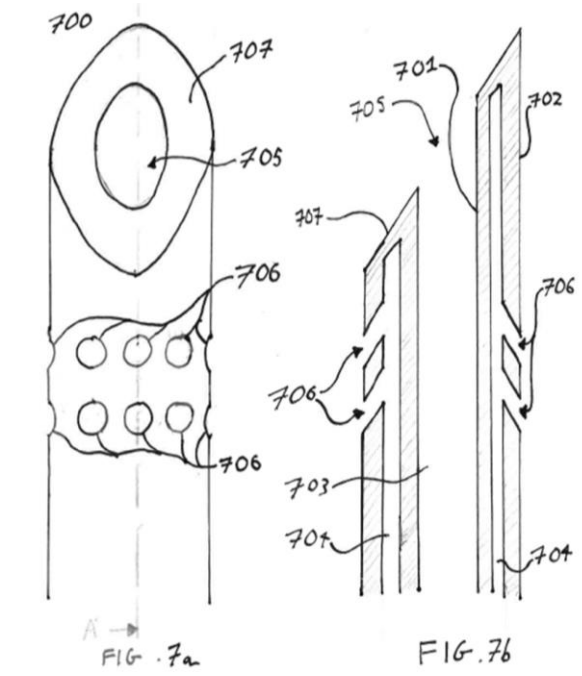
Cochrane Library
Cochrane Database of Systematic Reviews

Follicular flushing during oocyte retrieval in assisted reproductive techniques (Review)

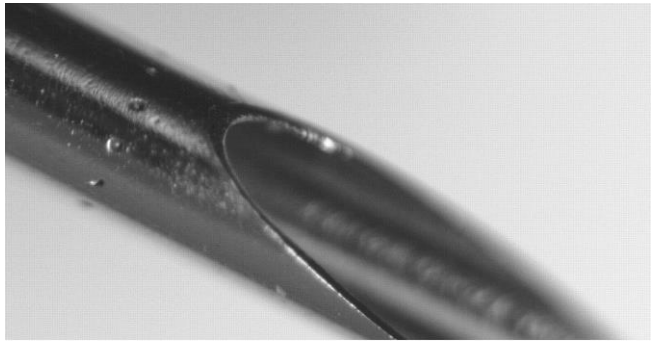
Georgiou EX, Melo P, Brown J, Granne IE

8. Georgiou EX, Melo P, Cheong YC, Granne IE. Follicular flushing during oocyte retrieval in assisted reproductive techniques. Cochrane Database Syst Rev. 2022 Nov 21;11(11):CD004634. doi: 10.1002/14651858.CD004634.pub4. PMID: 36409927.

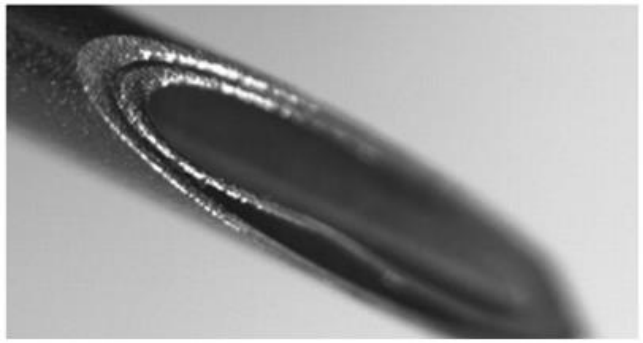
The OxIVF needle



(new patented[9] needle design with lateral flushing capabilities)



(current state-of-the-art)



[9] Vatish, M., Cimpeanu, R., Georgiou, E., & Castrejon-Pita, A. A. (2022). *U.S. Patent Application No. 17/762,865,* US20220323112A1 - Needle and uses thereof.

In silico computational modelling

We solve the incompressible, three-phase, Navier-Stokes equations with surface tension using the Volume-of-Fluid method.

$$\rho_i(\partial_t \mathbf{u}_i + \mathbf{u}_i \cdot \nabla \mathbf{u}_i) = -\nabla p_i + \nabla \cdot (2\mu_i \mathbf{D}) + \sigma_{ij}\kappa\delta_s \mathbf{n}$$

Conservation of momentum

$$\nabla \cdot \mathbf{u}_i = 0$$

Conservation of mass

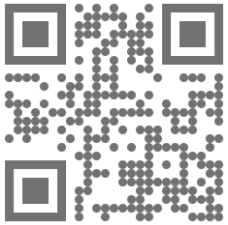
$$\rho = c_1\rho_1 + c_2\rho_2 + (1 - c_1 - c_2)\rho_3$$
$$\mu = c_1\mu_1 + c_2\mu_2 + (1 - c_1 - c_2)\mu_3$$

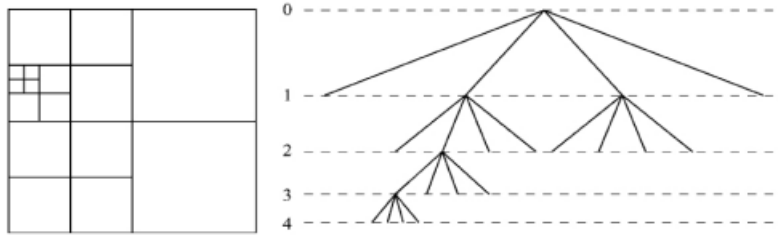
Multiphase flow modelling

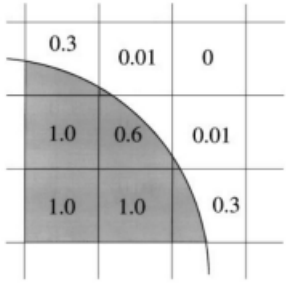
$$\partial_t c_i + \nabla \cdot (c_i \mathbf{u}) = 0$$

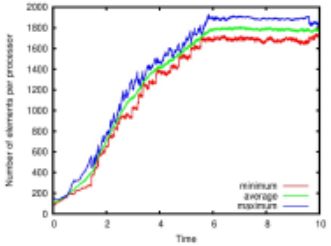
Volume fraction advection

- u: velocity
- p: pressure
- σ: surface tension coefficient
- μ: viscosity
- ρ: density
- κ: curvature
- n: interface normal
- c: volume fraction









(Popinet 2003, 2009, 2015)

In silico computational modelling

Recent publication (October 2023) in the Journal of Biomechanics[10]

Contents lists available at ScienceDirect

Journal of Biomechanics

journal homepage: www.elsevier.com/locate/jbiomech

A new flow-based design for double-lumen needles

Radu Cimpeanu [a,b,*], Alfonso A. Castrejón-Pita [c], Lee Nai Lim [d], Manu Vatish [e], Ektoras X. Georgiou [d]

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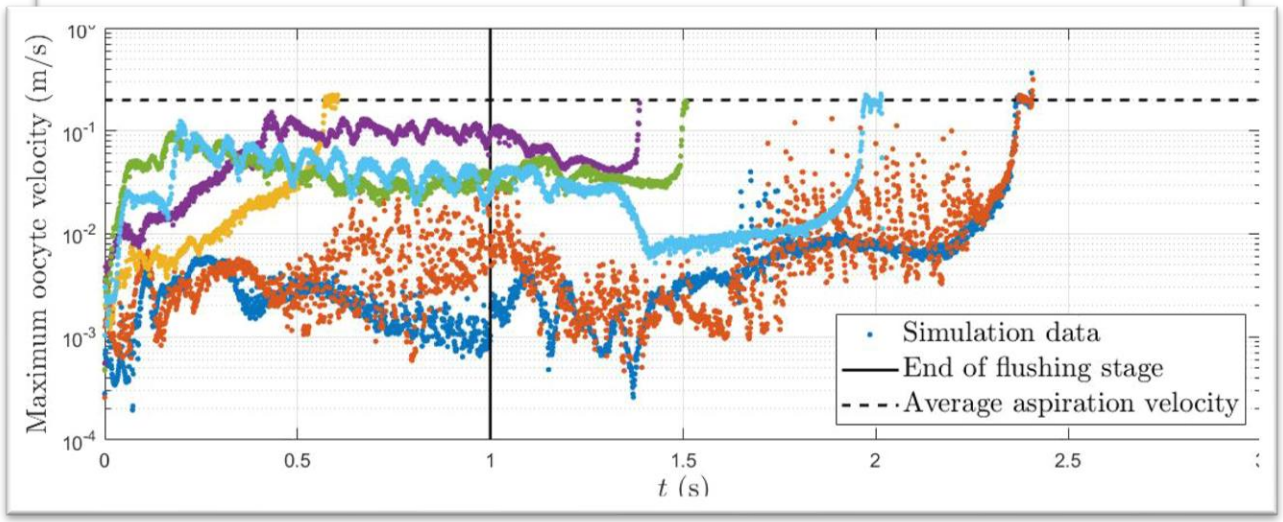
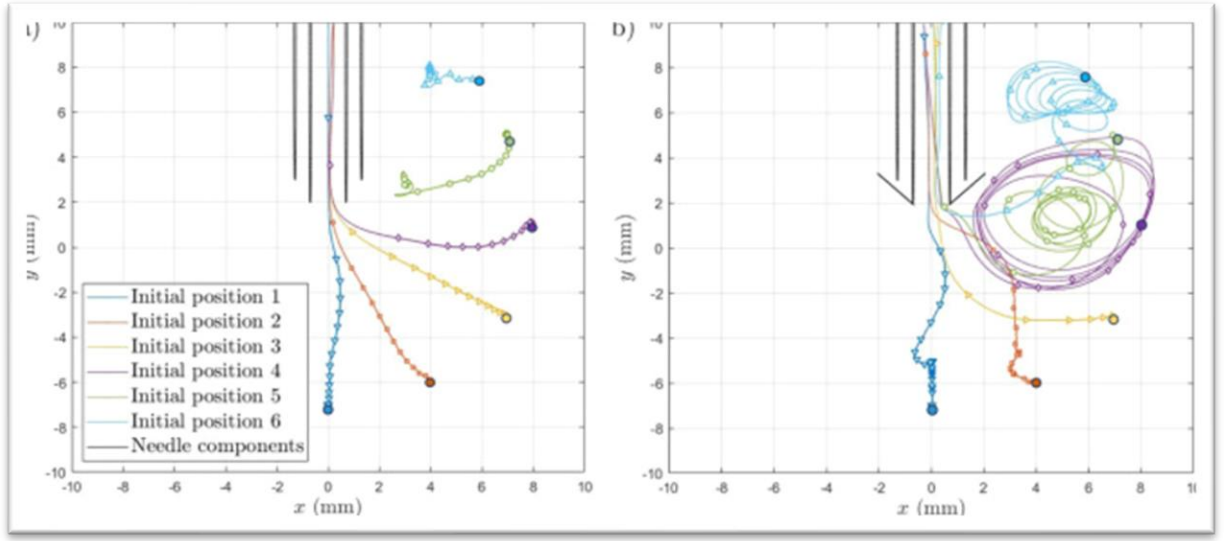
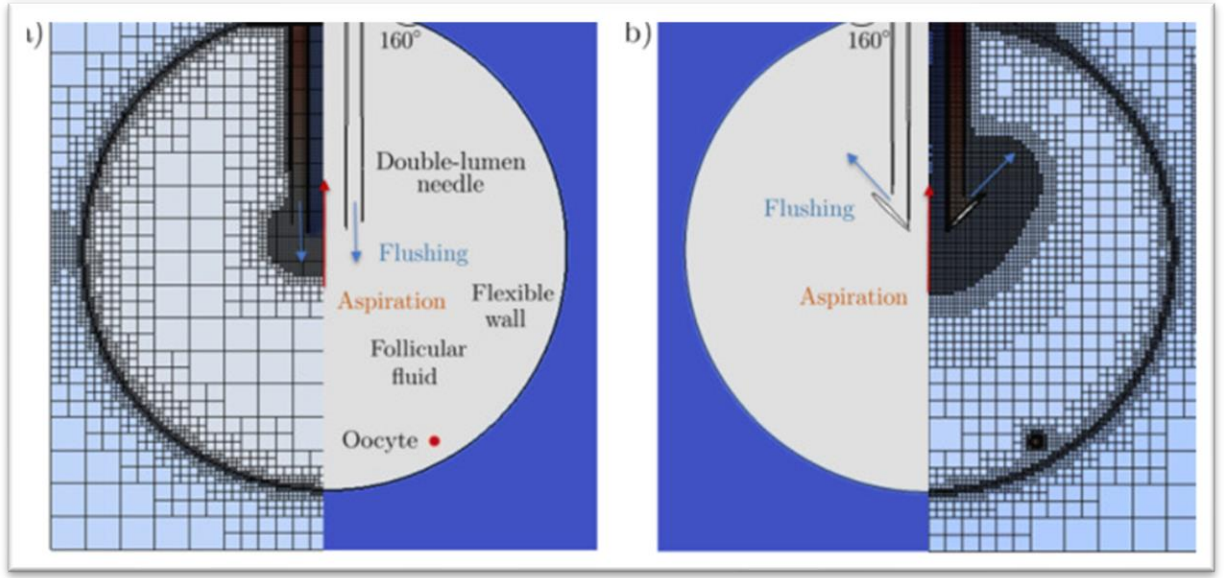
[e] Nuffield Department of Women's Health and Reproductive Research, University of Oxford, Oxford, OX3 9DU, United Kingdom







[10] Cimpeanu, R., Castrejón-Pita, A. A., Lim, L. N., Vatish, M., & Georgiou, E. X. (2023). A new flow-based design for double-lumen needles. *Journal of Biomechanics*, *160*, 111832.

Ex vivo pilot study[11]

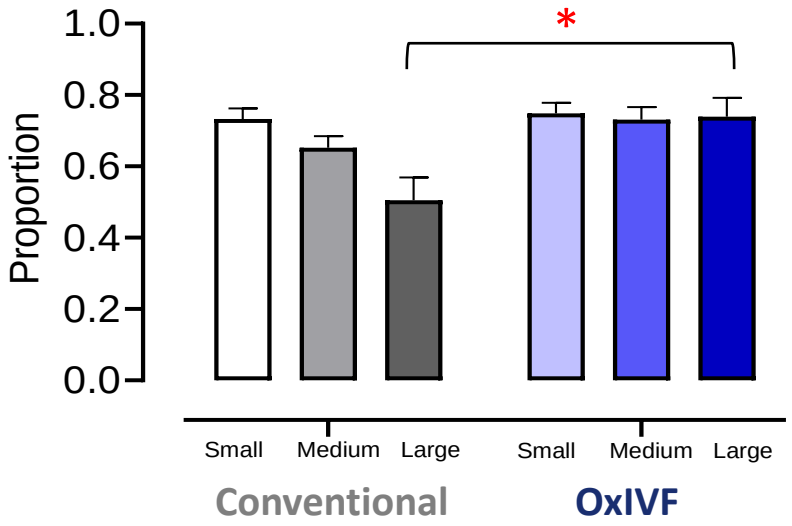
- Slaughterhouse cattle ovaries
- 3 groups:
  - Small: 7-10mm
  - Medium: 11-14mm
  - Large: >15mm
- Conventional dual channel needle vs OxIVF prototype
- Outcomes: oocyte yield & quality (IETS classification)

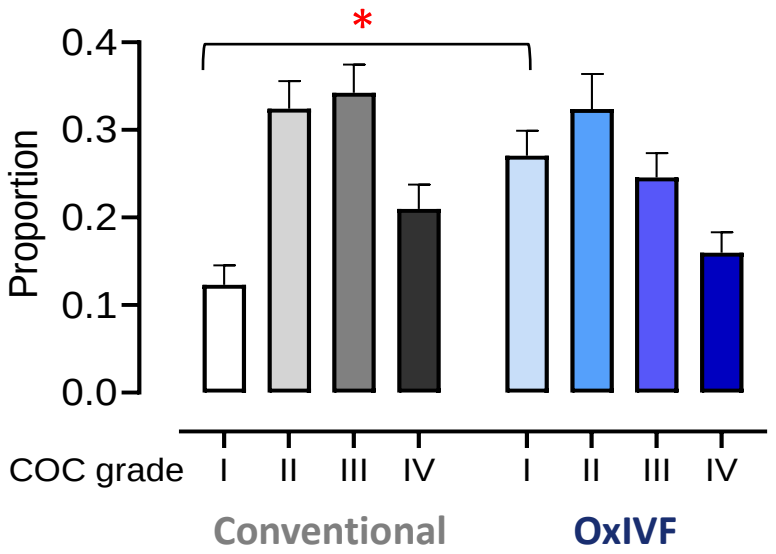
Overall oocyte yield: $p < 0.05$

- OxIVF: 74.1% ± 2.09
- Conventional: 67.0% ± 2.23

Grade I oocytes: $p < 0.001$

- OxIVF: 27.3% ± 2.71
- Conventional: 12.2% ± 2.16

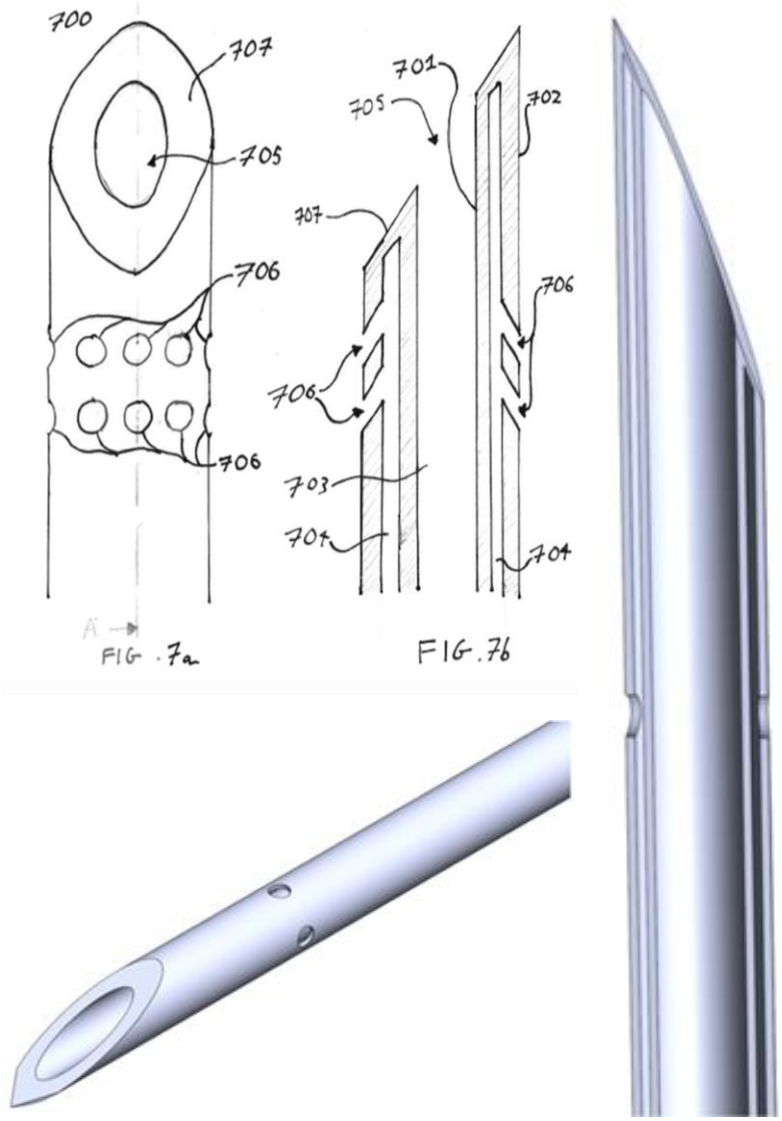




*: $p < 0.05$

[11] Simmons R. J. et al. (2023) Ovarian follicle flushing as a means of retrieving oocytes in bovine ovum pickup/*in vitro* production. *Reproduction, Fertility and Development* **35**, 228.

Future outlook



Ongoing work (watch this space) with colleagues at the University of Nottingham and the Paragon Veterinary Group indicates significant promise in terms of target metrics, including fertilization rate and morula and blastocyst rate, all pointing to a successful potential navigation of the OxIVF needle design towards real-life use.

Key conclusion: Significant improvement in oocyte yield and embryo development demonstrated in silico, ex vivo and in vivo.

Next steps – alongside activity in the veterinary space, focus on translation to humans:

- Regulatory aspects
- Commercialisation
- Clinical trials