# Adhesion of *Plasmodium falciparum* infected erythrocytes in *ex vivo* perfused placental tissue – a novel model of placental malaria

Caroline Pehrson[1*§], Line Mathiesen [2§], Kristine K Heno[1], Ali Salanti[1], Mafalda Resende[1], Ron Dzikowski[3], Peter Damm[4], Stefan R Hansson[5], Christopher L King[6], Henning Schneider[7], Christian W Wang[1], Thomas Lavstsen[1], Thor G Theander[1], Lisbeth E Knudsen[2], Morten A Nielsen[1*]

[1]Centre for Medical Parasitology at Department of Immunology and Microbiology, Faculty of Health and Medical Sciences, University of Copenhagen and at Department of Infectious Diseases, Copenhagen University Hospital (Rigshospitalet), Denmark

[2]Section of Environmental Health, Department of Public Health, University of Copenhagen, Øster Farimagsgade 5A, 1353 Copenhagen, Denmark, Denmark

[3]Department of Microbiology and Molecular Genetics, The Institute for Medical Research Israel - Canada, The Kuvin Center for the Study of Infectious and Tropical Diseases, The Hebrew University-Hadassah Medical School, Jerusalem 91120, Israel

[4]Department of Obstetrics, Rigshospitalet, Faculty of Health and Medical Sciences, University of Copenhagen, Blegdamsvej 9, 2100 Copenhagen Ø, Denmark.

[5]Division of Obstetrics and Gynecology, Department of Clinical Sciences Lund, Lund University, Sweden.

[6]Center for Global Health and Diseases, Case Western Reserve University and Veterans Affairs Medical Center, Cleveland, USA

[7]Department of Obstetrics and Gynecology, Inselspital, Bern University Hospital, University of Bern, Switzerland

[§]These authors contributed equally to this work

[*]Corresponding authors

Caroline Pehrson +45-35332909, cpeh@sund.ku.dk

Morten A Nielsen +45-35326803, mortenn@sund.ku.dk

**Additional file 1 - Quality and viability characteristics of perfusion experiments.**

| **Experiment** | **P211013** | **P141113** | **P091213** | **P171013** | **P211013-2** | **P241013** | **P100314[a]** | **P170314[a]** | **P200314[a]** | **P041113** |
|---|---|---|---|---|---|---|---|---|---|---|
| Maternal age (years) | 40 | 41 | 32 | 31 | | | 28 | 50 | 27 | 34 |
| Primipara | No | Yes | Yes | No | | | No | No | Yes | No |
| Newborn gender | F | M | F | F | F | M | M | F | M | F |
| Gestational age (weeks+days) | 38+0 | 39+2 | 38+2 | 38+4 | 38+1 | 39+2 | 38+2 | 39+0 | 39+1 | 39+0 |
| Newborn weight (g) | 3420 | 3712 | 2900 | 3166 | 3132 | 3944 | 3056 | 2872 | 3780 | 3670 |
| Placenta weight (g) | 706 | 649 | 691 | 818 | | 797 | 546 | 695 | 607 | 662 |
| Perfused cotyledon weight (g) | | | | | | | 19.2 | 25.3 | 36.9 | |
| Time from delivery to cannulation of fetal vessels (min) | 35 | 30 | 27 | 12 | | 36 | 31 | 34 | 18 | 40 |
| Volume change fetal circulation (ml/h) | 1.7 | -1.1 | -1.6 | 1.2 | -3.0 | -2.2 | -1.0 | -7.7 | -1.4 | -4.7 |
| Volume change maternal circulation (ml/h) | -1.3 | -1.8 | -2.0 | 2.2 | -1.3 | -0.3 | 2.2 | 3.5 | -3.7 | 2.5 |
| Flow rate fetal circulation (ml/minute) | 3.2 | 3.0 | 2.8 | 3.5 | 3.6 | 2.9 | 2.7 | 3.0 | 2.7 | 2.8 |
| pH maternal[b] | 7.32±0.08 | 7.35±0.02 | 7.25±0.05 | 7.33±0.12 | 7.33±0.08 | 7.39±0.08 | 7.33±0.06 | 7.45±0.05 | 7.37±0.07 | 7.41±0.03 |
| pH fetal[b] | 7.31±0.08 | 7.41±0.02 | 7.35±0.09 | 7.35±0.11 | 7.36±0.06 | 7.34±0.03 | 7.24±0.06 | 7.38±0.03 | 7.40±0.02 | 7.45±0.01 |
| $pO_2$ maternal (kPa)[b] | 17.7±1.0 | 14.0±2.5 | 14.1±4.6 | 14.8±1.5 | 14.9±3.2 | 9.5±2.8 | 19.8±0.8 | 21.1±0.8 | | 14.2±2.3 |
| $pO_2$ fetal inflow (kPa)[b] | 5.8±5.2 | 9.7±4.5 | 4.6±2.8 | 3.4±2.4 | 4.4±3.1 | 6.0±5.7 | 3.7±1.8 | 7.6±1.7 | | 7.0±4.2 |
| $pO_2$ fetal outflow (kPa)[b] | 8.0±1.8 | 8.0±2.5 | 8.8±4.0 | 5.8±1.4 | 6.1±1.1 | 6.8±1.8 | 9.2±2.5 | 6.8±2.5 | | 9.1±2.3 |
| Glucose uptake maternal (µmol/L/min)[c] | 39.5±10.1 | | 45.4±11.2 | 29.0±10.1 | 47.4±10.4 | 35.9±7.5 | 18.3±9.5 | 14.7±5.7 | 45.1±10.4 | 33.8±8.2 |
| Glucose uptake fetal (µmol/L/min)[c] | | | 20.5 | | 25.0±0.8 | 5.4 | 7.7±0.8 | 4.1±0.4 | 7.8±9.7 | 3.0±1.9 |
| Lactate release maternal (µmol/L/min)[c] | 88.2 | | 102.7±24.5 | 57.4±9.2 | 102.5 | 59.0 | 47.9±11.8 | 24.6±25.3 | 92.2±16.0 | 74.2±14.4 |
| Lactate release fetal (µmol/L/min)[c] | | | 28.2±7.3 | 22.6 | 48.7 | | 16.9±3.7 | 16.0±7.6 | 19.8±5.7 | -0.1±15.1 |

| **Experiment** | **P111113** | **P181113** | **P030414**[a] | **P070414**[a] | **P240314**[a] | **P270314**[a] | **P310314**[a] | **P220514**[a] | **P260514**[a] | **P170714**[a] |
|---|---|---|---|---|---|---|---|---|---|---|
| Maternal age (years) | 31 | 31 | 34 | 36 | 35 | 36 | 35 | | 40 | 38 |
| Primipara | No | No | No | No | No | No | No | | Yes | No |
| Newborn gender | F | F | F | M | F | M | M | | F | M |
| Gestational age (weeks+days) | 38+0 | 38+0 | 39+0 | 38+4 | 38+5 | 39+0 | 38+2 | | 40+6 | 38+4 |
| Newborn weight (g) | 3068 | 3774 | 3274 | 3634 | 2826 | 3800 | 3752 | | 3970 | 3980 |
| Placenta weight (g) | 608 | 658 | 714 | 968 | 535 | 735 | 692 | | 643 | 925 |
| Perfused cotyledon weight (g) | | | 17.4 | 16.4 | 16.2 | 7.9 | 12.4 | 28.0 | 24.2 | |
| Time from delivery to cannulation of fetal vessels (min) | 28 | 24 | 31 | 32 | 32 | 29 | 28 | | 29 | 25 |
| Volume change fetal circulation (ml/h) | -1.0 | -0.8 | -9.7 | -1.0 | -9.0 | -0.4 | -4.9 | 0.7 | -3.1 | 0.1 |
| Volume change maternal circulation (ml/h) | -2.3 | -3.3 | -3.8 | 0.4 | -0.6 | -19 | -0.9 | -2,0 | 1.5 | -2.6 |
| Flow rate fetal circulation (ml/minute) | 3.1 | 3.1 | 3.1 | 3.0 | 3.1 | 3.1 | 3.2 | 3.5 | 3.3 | 3.1 |
| pH maternal[b] | 7.37±0.06 | 7.32±0.07 | 7.44±0.06 | 7.38±0.04 | 7.45±0.05 | 7.42±0.05 | 7.36±0.04 | 7.43±0.07 | 7.42±0.07 | 7.35±0.09 |
| pH fetal[b] | 7.42±0.03 | 7.46±0.02 | 7.33±0.04 | 7.32±0.05 | 7.45±0.03 | 7.47±0.01 | 7.41±0.02 | 7.40±0.06 | 7.44±0.01 | 7.38±0.01 |
| $pO_2$ maternal (kPa)[b] | 15.0±3.3 | 15.0±0.8 | 21.0±0.6 | | | | | 18.8±1.6 | 18.7±1.5 | 17.2±2.6 |
| $pO_2$ fetal inflow (kPa)[b] | 8.0±5.1 | 8.0±4.2 | 6.4±0.9 | 9.6±2.6 | | | | 6.5±2.6 | 6.3±2.3 | 5.5±2.1 |
| $pO_2$ fetal outflow (kPa)[b] | 11.5±1.0 | 9.4±1.7 | 7.5±1.7 | | | | 17.9±0.4 | 7.2±4.0 | 6.2±1.6 | 7.6±3.1 |
| Glucose uptake maternal (µmol/L/min)[c] | | | 11.4±5.2 | 31.7±4.5 | 19.9±3.3 | 32.1±10.6 | 29.2±12.1 | 50.4±11.1 | 45.4±11.5 | 48.0±11.5 |
| Glucose uptake fetal (µmol/L/min)[c] | | | 5.5±5.1 | 16.4±10.3 | 3.9±12.1 | 1.4±5.5 | 3.4±2.6 | 12.4±9.9 | 10.0±7.1 | 6.8±2.6 |
| Lactate release maternal (µmol/L/min)[c] | | | 33.3±6.7 | 70.6±11.5 | 38.4±5.2 | 69.3±12.6 | 54.9±24.8 | 105.2±14.6 | 94.2±20.4 | 99.1±16.8 |
| Lactate release fetal (µmol/L/min)[c] | | | 13.7±2.5 | 9.4±5.1 | 1.0±11.1 | 6.9±2.3 | 7.7±6.7 | 28.5±13.4 | 6.7±12.1 | 10.5±3.2 |

[a]Experiments performed with an oxygenator equilibrating the medium with atmospheric air inserted in the maternal circulation
[b]Mean ± standard deviation
[c]Mean ± standard deviation of stabilisation and experimental phases (if data was available from one phase only, uptake/release between first and last measurements is shown)