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Dynamic contrast enhanced magnetic resonance imaging: A review of its application in the assessment of placental function

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► To cite this version:

Mathilde Jacquier, Chloé Arthuis, David Grévent, Laurence Bussièrès, Charline Henry, et al.. Dynamic contrast enhanced magnetic resonance imaging: A review of its application in the assessment of placental function. *Placenta*, 2021, 114, pp.90-99. 10.1016/j.placenta.2021.08.055 . hal-03790050

HAL Id: hal-03790050

<https://hal.inrae.fr/hal-03790050>

Submitted on 16 Oct 2023

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1 *** Title Page and Abstract**

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3 **Title Page**

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5 **Full title:** Dynamic contrast enhanced magnetic resonance imaging: a review of its
6 application in the assessment of placental function

7

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Abbreviations:

AIF: Arterial Input Function The concentration of a tracer, in this case gadolinium based contrast agent, in blood/plasma over time.

ASL: Arterial Spin Labeling, an MRI technique used to measure blood flow in which contrast agents are not needed, but rather magnetic pulses are used to label blood as it flows into the area of interest.

BOLD-MRI: Blood Oxygen Level Dependent, a non-invasive in-vivo technique of placental oxygenation assessment using hemoglobin as an endogenous contrast agent.

DCE-MRI: Dynamic Contrast Enhanced Magnetic Resonance Imaging MRI technique in which an exogenous intravascular contrast agent is administered and the passage of this contrast agent through tissues is dynamically imaged by obtaining serial images over time.

ED: Embryonic Day

EPI: Echo planar imaging

FBV: placental fractional blood volume

GCTT: Gamma capillary transit time, a mathematical model used to calculate functional MRI parameters

Gd-CA: Gadolinium-based contrast agents

HPZ and LPZ: high-flow zone and low-flow zone, two functional spaces of the murine placenta

IVIM: Intravoxel Incoherent Motion: MRI techniques in which attempts are made to account for the signal contributions from all motion at microscopic levels, namely perfusion at microvascular levels as well as diffusion into tissues, and provides information about tissue microcirculation and also diffusion related to tissue microstructure.

PBF: Placental blood flow (F= $\text{mL}/\text{min}/100\text{mL}$)

PS: Permeability surface area ($\text{mL}/\text{min}/\text{g}$)

SPIO: Super Paramagnetic Iron Oxides

T1-FFE: Fast Field Echo; FLASH: Fast Low Angle Shot; SPGR: Spoiled Gradient Recalling imaging: MRI sequences using gradient-spoilers destroying the residual transverse magnetization to optimize T1-weighting.

Vb: Fractional blood volume (%)

86 T1W images: T1 weighing of an image, is one in which the differences in tissue contrast is
87 displayed on images based largely on the difference in T1 relaxation times of tissues. Such
88 images are one of the fundamental methods of displaying MRI images and can be acquired
89 using a broad spectrum of MRI sequences
90

91 DW imaging: Diffusion-weighted magnetic resonance imaging is a form of MR imaging based
92 upon measuring the random Brownian motion of water molecules within a voxel of tissue.
93

94 SNR : Signal to noise ratio
95

96 CNR : Contrast to noise ratio
97

98 CA : Contrast agent
99

100

101 **Abstract:**

102 It is important to develop a better understanding of placental insufficiency given its role in
103 common maternofetal complications such as preeclampsia and fetal growth restriction.

104 Functional magnetic resonance imaging offers unprecedented techniques for exploring the
105 placenta under both normal and pathological physiological conditions. Dynamic contrast-
106 enhanced magnetic resonance imaging (DCE MRI) is an established and very robust method
107 to investigate the microcirculatory parameters of an organ and more specifically its
108 perfusion. It is currently a gold standard in the physiological and circulatory evaluation of an
109 organ.

110 Its application to the human placenta could enable to access many microcirculatory
111 parameters relevant to the placental function such as organ blood flow, fractional blood
112 volume, and permeability surface area, by the acquisition of serial images, before, during,
113 and after administration of an intravenous contrast agent. Widely used in animal models
114 with gadolinium-based contrast agents, its application to the human placenta could be
115 possible if the safety of contrast agents in pregnancy is established or they are confirmed to
116 not cross the placenta.

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***Highlights**

Highlights

1. DCE-MRI is a very robust method to investigate the microcirculatory parameters.
2. DCE-MRI provide extraordinary range of data on the placental function.
3. The future of DCE-MRI lies in the widespread availability of safe contrast agents.
4. Perspectives can be envisaged with the combination of several functional-MRI techniques.

*Manuscript References

Manuscript

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168 Introduction:

169 The current challenge in placental imaging is to improve our knowledge of its function. One
170 of the essential parameters of the placental function is its perfusion. A more precise
171 understanding of placental perfusion is of great interest as under-perfusion or placental
172 insufficiency, could result in intrauterine growth restriction or perinatal death [1-3]. The
173 study of placental permeability is also of great importance, since the placenta is the only
174 organ that allows the exchange between the mother and the fetus. Altered permeability
175 could be a key factor in placental pathophysiology in the event of insufficient transfer of
176 nutrients to the fetus [4-7].

177 An approach to placental function can be achieved by ultrasound, a tool used as first line in
178 current practice but remains limited in the assessment of the intervillous space and
179 uteroplacental circulation. Various functional placental MRI techniques have been
180 developed for two decades. All aim at providing information on placental perfusion,
181 sometimes only semi-quantitatively (IVIM), but only one, covered in this review, allows
182 quantitative characterization of both perfusion and other functional parameters such as
183 permeability and fractional blood volume: Dynamic Contrast Enhanced Imaging (DCE). DCE
184 MRI is an established and very robust method to investigate the microcirculatory parameters
185 of an organ, ~~including and more specifically~~ its perfusion. It is currently a gold standard in the
186 physiological and circulatory evaluation of an organ. Its application to the human placenta
187 could enable to access many microcirculatory parameters relevant to the placental function.
188 Often criticized for its complexity, we initially hope to clarify the basics of this technique. We
189 will then discuss the different contrast agents available, followed by a review the main
190 results it provides on the fundamental parameters of placental functionality: perfusion,
191 permeability and fractional blood volume. Finally, we discuss potential future applications of
192 this technique.

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197 **Fundamentals**

198 Basic concept of DCE-imaging

199 DCE-MRI is based on the analysis of tissue enhancement kinetics after intravenous injection
200 of a contrast agent. Serial T1-weighted acquisitions are carried out throughout the
201 intravenous injection of a contrast agent : 1) Anatomical un-enhanced images are acquired
202 before injection to obtain base-line signal values in the vasculature and tissues in the regions
203 of interest 2) Images are acquired as the bolus of contrast agent first arrives in the arterial
204 system allowing demonstration and calculation of an Arterial Input Function (AIF) 3) Finally,
205 images are acquired as the contrast agent passes through and washes out of tissues and
206 tissue enhancement fades and reaches a steady state (Figure 1) [8-10].

207 The kinetics of tissue enhancement reflects two basics physiological phenomena: the tissue
208 perfusion and the leakage of the CA into the interstitial space described in detail by Cuenod
209 and Balvay [11].

210 The tissue enhancement kinetics give us information about several physiological parameters
211 of the microcirculation (Figure 2). The initial rise of the curve depends on the tissue
212 **perfusion** blood flow **rate**, that is to say the **tissue-blood** flow entering and exiting a volume
213 of tissue (FT, expressed in mL of blood/min/100 mL tissue). **FT corresponds to the ambiguous**
214 **term of “perfusion”**. Then, the early peak reflects the tissue blood volume (also referred to
215 as blood volume fraction) which corresponds to the volume of capillary blood contained in a
216 certain volume of tissue (Vb, mL blood/100 mL of tissue or in %). The kinetics after the peak
217 depend on the permeability, the flow of molecules through the capillary membranes in a
218 certain volume of tissue (surface area product PS, in mL/min/100 mL tissue). Finally, the
219 later part of the curve depends on the tissue interstitial volume, also known as the
220 extravascular and extracellular volume fraction (Ve, %). [11, 12].

221

222 DCE-MRI acquisition: basic protocol, data pre-processing and optimizations

223 Fast gradient echo T1-weighted sequences are mostly used with gradient-spoilers destroying
224 the residual transverse magnetization (T1-FFE, FLASH, SPGR, RF spoiled FE).

225 The parameters of these sequences (low flip angle, short repetition time, increased receiver
226 bandwidth) are associated with a low SNR (signal to noise ratio). Considering that SNR has a
227 very important influence on DCE-MRI pharmacokinetic modeling, with higher SNR increasing

228 the precision with which parameters can be evaluated [13], enhancing SNR is of great
229 importance. Choosing the optimal flip angle is found by many authors [13-16] to be one
230 solution to obtain a higher SNR. A compromise between spatial-temporal resolution, SNR
231 and CNR (contrast to noise ratio) remains a major challenge-

232 Unlike in DCE-CT, enhancement values and concentration of contrast agent do not follow a
233 linear relationship in DCE-MRI. Many strategies have been developed to improve this
234 conversion and are summarized by Cuenod [11].

235

236 **Contrast agents:**

237 The contrast agent (CA) is considered to have the properties of a tracer, that is to say it does
238 not modify either the volumes of the compartments over time or the physiological
239 conditions of the system. The mixing of a CA is considered instantaneous and homogeneous
240 inside each compartment. MRI contrast agents may be categorized according to their
241 magnetic properties, chemical composition, route of administration, effect on the magnetic
242 resonance image, biodistribution and application. Their classification and application have
243 been the subject of a review by Xiao [17].

244

245 **Conventional use of Gadolinium based contrast agent (Gd-CA) in clinical practice:**

246 Gadolinium chelates are paramagnetic contrast agents that shorten T1 and T2 relaxation
247 times. Their placental pharmacokinetics in animal models are well established: a placental
248 wash-out has been quantified at 50% one hour after injection in rabbits and at 99% 24 hours
249 after injection in rats [18,19]. In the human placenta, only qualitative data describe an early
250 placental enhancement with a quick wash-out compared to the myometrium [20].

251 Gadolinium

252 chelates then reach the fetal blood and are excreted through the urine in the amniotic fluid
253 [18]. This accumulation in the amniotic fluid is poorly documented. Possible reabsorption in
254 the fetal lungs or digestive tract [18] raises concerns of potential toxicity [21,22]. Although
255 the administration of Gadolinium appears safe in the first trimester [22, 23], a large
256 epidemiological study by Ray et al [22] of over 1.4 million deliveries in Canada suggested
257 that exposure during the second and third trimesters may carry greater risks of
258 rheumatologic-inflammatory like conditions (adjusted hazard ratio, 1.36; 95% confidence
259 interval [CI], 1.09–1.69) and stillbirth or neonatal death (adjusted relative risk, 3.70; 95% CI,

260 1.55–8.85). Despite undisputed strengths, this large registry study lacks relevant clinical
261 history, including co-morbidities and the indications for performing the MRI studies in
262 pregnancy. MRI studies would have been performed in pregnancy for specific clinical
263 indications, including: (i) early and unknown pregnancy, therefore increasing potential
264 adverse consequences, and (ii) maternal-fetal conditions necessitating MRI despite the
265 pregnancy. Fraum et al [24] summarized the international guidelines regarding the use of
266 Gd-CA in pregnancy: the current consensus is to restrict its use to cases where the maternal-
267 fetal benefits outweigh the potential risks after a case-by-case analysis.

268

269 Alternative contrast agents used in research

270 To overcome the uncertainty about gadolinium safety [21,22], other contrast agents that
271 remain in the intravascular space have been developed. Establishing their safety and
272 widespread use is the main challenge to the generalization of the use of the DCE-MRI in
273 human pregnancy in the coming years. The principal characteristics of Gd-CA, liposomal-Gd
274 and SPIO agents are summarized in table 4. Other contrast agents such as manganese
275 complexes have also been developed [25].

276

277 Liposomal gadolinium [26-36]

278 Liposomal-Gd agents have important biological and physical characteristics distinguishing
279 them from common GBCA: (1) a large size (100–150 nm diameter, molecular weight~ 2 Å~
280 105 kD) gives them a long in vivo half-life and a low propensity to extravasate [26-28] and (2)
281 a high T1-relaxivity [29-31]. These properties result in an extended imaging window for
282 acquisition of high-resolution images rich in SNR and CNR [32]. Liposomal-Gd contrast agents
283 have different molecular structures, typically either core-encapsulated nanoparticles
284 (encapsulated gadolinium within the core-interior) or surface-conjugated nanoparticles
285 (gadolinium conjugated on the surface). Ghaghada described a Dual-Gd agent (a
286 nanoparticle that has both core-encapsulated and surface-conjugated gadolinium), with
287 improved SNR and CNR [32]. It has been demonstrated that liposomal-Gd does not
288 penetrate the placental barrier in animal models [32-36]. In 24 normal-growth fetoplacental
289 units, Badachape [36] reports the ability of liposomal-Gd contrast agents to provide an
290 accurate estimation of placental fractional blood volume (FBV) with increasing values as
291 gestation progresses. To our knowledge, there is no data about their use in human placenta,

292 and maternal and fetal safety remains to be established. This contrast agent could have the
293 advantage of quantifying only maternal perfusion into intervillous space. However fetal
294 pharmacokinetics or placental permeability may not be evaluated by this type of contrast
295 agent.

296

297 SPIO (Super Paramagnetic Iron Oxides) [37-41]

298 Iron oxide nanoparticles were first developed for the treatment of anemia and have recently
299 received substantial interest as an MRI contrast agent due to their T1 and T2 relaxation time
300 shortening properties. Unlike Gd-CA, Ferucarbotran and Ferumoxytol, the two main such
301 agents, have a long intravascular half-life (14h for ferumoxytol vs 1.6h for Gd-CA), which
302 results in a long blood pool phase prior to detectable contrast extravasation. Several studies
303 have shown that neither Ferucarbotran nor Ferumoxytol cross the placental barrier [39-41].
304 Ferucarbortran-enhanced MRI was used by Deloison et al [41] who showed its capacity to
305 measure placental perfusion and permeability in both physiological and pathological settings
306 in a rat model of chronic hypoxia that led to intrauterine growth restriction (placental blood
307 flow in the ligated horns compared to the normal horns (108.1 versus 159.4 mL/minute/100
308 mL, $p = 0.0004$)). Two studies [39,40] demonstrated the feasibility of ferumoxytol-enhanced
309 MRI in pregnancy with a nonhuman primate model. ~~R2* mapping and quantitative~~
310 ~~susceptibility mapping in a pregnant nonhuman primate model.~~

311

312 **Data Analysis**

313

314 Enhancement data can be analyzed with qualitative, semi-quantitative or quantitative
315 methods. These three approaches are described below in order of increasing complexity.

316

317 Qualitative analysis:

318 This is the most subjective method based on an operator's interpretation. Routinely used in
319 breast imaging [42], the qualitative analysis consists of describing the enhancement by its
320 intensity, its speed, and its homogeneous or heterogeneous appearance [9,43]. Although not
321 quantitative, its simplicity gives it advantages (less sensitivity to variations in sequence
322 parameters, no requirement in terms of calculation) [12].

323

324

325

326 Semi-quantitative analysis:

327 It consists of evaluating quantitative parameters from the time-intensity curve. Various
328 parameters, including the maximum (relative) enhancement (%), the time to peak (in
329 seconds), the rate of peak enhancement (%), the maximum slope of the curve fit function
330 and the area under the curve (AUC), could be calculated for each ROI [44-46]. This analysis
331 makes it possible to compare different placental perfusion profiles (i.e placental
332 insufficiency) but does not, for example, provide a flow rate in mL/min/dL.

333

334 Quantitative analysis:

335 This method makes it possible to quantify the flow rate of the intervillous space, in order to
336 establish reference values for a normal pregnancy at a given gestational age. This method
337 must take into account that the contrast agent acts as a tracer and is therefore found
338 simultaneously in the placenta and the fetus.

339 Models to evaluate flow rate have been established. They need the definition of an arterial
340 input function (AIF) and must be adapted to the acquisition conditions.

341

342 *AIF (arterial input function):*

343 AIF is the estimation of the contrast agent concentration in an afferent artery as a function
344 of time. A requirement of almost all quantitative analysis methods, a wide variety of
345 strategies to measure it have been described. The most invasive one consists of introducing
346 an arterial catheter to sample blood during the imaging process for later analysis [47-48].
347 Deemed impractical due to its invasive nature, simpler methods assume that the AIF is
348 similar for all subjects [49], but the inter- and intrasubject variations in AIF leads to large
349 systematic errors in the analyses [50-51]. The AIF can also be collected from the DCE-MRI
350 data set; giving an accurate and individual AIF measure, this method requires the presence
351 of a large vessel within the field of view, which is not always the case. If no vessel is
352 available, a mean AIF corresponding to an average value obtained in a population can be
353 used as described by Parker [52]. Finally, Yankeelov suggested a method of quantitative
354 pharmacokinetic analysis of DCE-MRI data without knowledge of the AIF [53].

355

356

357

358 *Design of the acquisition protocol depending on the desired parameters*

359 The ability to study microcirculatory parameters depends on the acquisition conditions.
360 Parameters about tissue blood volume and capillary permeability only require intermediate
361 frame rates and acquisition time, whereas high temporal resolution and long acquisition
362 time permit the study both perfusion and permeability parameters [11]. The acquisition
363 protocol therefore must be designed according to the parameters studied.

364

365 *Models*

366

367 Given that MRI contrast agents acts as a tracer, to study and quantify blood flow a
368 compartmental analysis is required. The placenta is considered as a two- or three-
369 compartment organ comprising a tissue compartment, a blood compartment, and an
370 interstitial compartment, depending on the organ and the species studied [54-56]. This is
371 especially important for the placenta because different studies are comparing animal models
372 and the mouse/rat placenta is quite different than the macaque/human placenta. Even
373 though their overall function is the same, the compartments in these different species are
374 quite different.

375 The range of models available differ by their complexity. The more complex the model, the
376 more it closely follows physiology, with an unfortunate decrease in accuracy. Initial models
377 described, the Tofts-Ketty model and Brix model [59-60] have two-fittings parameters:
378 K_{trans} , the volume transfer constant between blood plasma and extravascular extracellular
379 space (EES) and V_e , the volume of EES per unit volume of tissue. As these models are not
380 suitable for analyzing data acquired with a rapid temporal resolution [11], other
381 physiological models have emerged.

382 Thus, the three-compartment model analysis is based on the underlying physiological
383 principle that the placenta is a countercurrent exchange system between the maternal and
384 fetal compartments [61]. The maternal vascular compartment of the placenta is supplied by
385 the arterial input (the uterine arteries) and drained by the venous output (Figure 3). The
386 fetal vascular compartment of the placenta is directly connected to the fetus [62]. The

387 exchanges between compartments, governed by concentration gradients, are described
388 using transfer constants according to the following equation:

$$389 \quad dq_2/dt = k(2.1) \cdot q_1(t) - k(0.2) \cdot q_2(t)$$

390 ~~The concentration in the intervillous space depends on the amount in the general maternal~~
391 ~~circulation as well as the rates of arterial input and venous draining.~~ Exchanges between
392 compartments (q_1 : arterial input, q_2 and q_3 : maternal and fetal compartment of the
393 placenta, q_4 : fetus) are governed by concentration gradients (k). q represents the quantity of
394 contrast medium of each compartment.

395 The steepest slope model, another quantitative model first described by Miles [63], is a
396 gradient-based approach to quantify perfusion, based on the initial uptake phase of the
397 contrast in the target organ. An arterial input function is defined, which is usually at the
398 hilum of the kidney to avoid pulsation artifacts within larger blood vessels. After 3D-
399 segmentation of the placenta and a baseline signal correction for each concentration time
400 curve of the DCE image sequence, the tissue perfusion is quantified from the following
401 equation [63]:

$$402 \quad F = \max(C'(t)) / \max(AIF(t))$$

403 where $C'(t)$ is the time-differential of the concentration-time curve, and $AIF(t)$ is the
404 previously defined arterial input function.

405 Another approach is the gamma capillary transit time (GCTT) model described by Schabel
406 [64], a generalized impulse response model for DCE-MRI that mathematically unifies the
407 Tofts-Kety, extended Tofts-Kety, adiabatic tissue homogeneity, and two-compartment
408 exchange models. This is achieved by including a parameter ($\alpha-1$) representing the width of
409 the distribution of capillary transit times within a tissue voxel. The GCTT model was utilized
410 for analysis due to its ability to account for heterogeneity in intravoxel contrast reagent
411 transit times [65].

412 Finally, based on the GCTT model, Frias et al. [65] developed an intervillous space
413 segmentation to quantify blood flow within individually identified cotyledons and three-
414 dimensionally maps the placental structure in a way that is consistent with the placental
415 histopathologic structure.

416

417 **Main results of the micro-circulatory parameters**

418

419 Tissue blood flow (FT) and fractional blood volume (Vb) in normal physiological
420 conditions

421 Despite heterogenous acquisition protocols, consistent results found a mean \pm standard
422 deviation FT value of 130 ± 50 mL/min/100 mL [67-68] and a mean maternal volume fraction
423 (Vb) of 36.5% [67, 68] (Table 1).

424 Two studies have separated the analysis of perfusion between the functional compartments
425 (HPZ and LPZ) of the placenta [69-70]. They found a significantly higher perfusion in the high-
426 flow compartment (HPZ) compared to the low-flow compartment (LPZ) ($p < 0.002$). In fact,
427 the caliber of the vessels and therefore the enhancement kinetics differ in those different
428 regions. However, the perfusion trends of the whole placenta are similar to those seen when
429 the placenta was studied by region. The data on the evolution of these two functional
430 perfusion parameters with gestational age differ. While Yadav et al [70] found a statistically
431 significant increase in perfusion of the whole placenta and HPZ ($p=0.02$ and $p<0.05$
432 respectively) as the pregnancy progresses, Remus et al [69] found no such statistically
433 difference in either compartment at Embryonic Day (ED) 14.5 and ED16.5 ($p=0.103$ and
434 $p=0.092$ respectively).

435 Unlike the murine model, the primate model shares essential placental anatomical features
436 with the human model (hemochorial placenta and cotyledon structure), which makes this
437 model particularly relevant. Frias et al [65] sought to develop a model as close as possible to
438 the histopathological structure of the placenta and successfully developed a DCE-MRI
439 protocol in primates that quantifies blood flow in individually identified cotyledons. They
440 found a mean \pm SD volumetric flow rate through each perfusion domain of 27.5 ± 10.0
441 mL/min with considerable variation (from 9.03 to 44.9 mL/min).

442

443 Tissue blood flow (FT) and fractional blood volume (Vb) in pathological conditions

444 Pathological conditions that decrease placental blood flow can be induced either by
445 exogenous means including pharmacological models [71], biological models [72] and surgical
446 models [68,73], or by endogenous ones [74, 76].

447 The comparison of placental blood flow (PBF) between pathological groups and controls
448 have been investigated in seven studies [41, 68, 71-75] (Table 2). Two studies [71,73]
449 reported a decreased PBF in the pathology group ($p<0.001$ and $p=0.0012$ respectively) while
450 Lemery et al [72] found no difference in a L-NAME model reproducing preeclampsia-like

451 conditions ($p = 0.496$). Interestingly, Remus et al [74] found an early decrease in PBF in a
452 group exposed to acoustic-stress at ED14.5 (123 ± 21 vs 147 ± 31 mL/min/100 mL; $p. 0.04$)
453 followed by a subsequent increase to ED 16.5 (192 ± 51 vs 141 ± 29 mL/min/100 mL, $p.$
454 0.001). This suggests that compensatory mechanisms could be involved. In this regard, three
455 studies [77-79] all show a decrease in vessel density in the labyrinthine zone in early
456 pathological states (ED 14.5) followed by a subsequent increase in vessel density to ED16.5
457 [41,42]. In a L-NAME model of placental hypoperfusion, Tarrade et al [79] found another
458 compensatory mechanism with an increased proportion and surface density of maternal
459 blood space in the L-NAME groups. The different models are therefore able to highlight
460 differences in perfusion in the pathology groups compared to the control groups.

461

462 Permeability:

463 DCE-MRI offers the unique possibility to assess placental permeability, that is to say is the
464 flow of molecules through the capillary membranes in a certain volume of tissue
465 (mL/min/100 mL tissue). The evaluation of the permeability is particularly interesting for
466 therapeutic studies or to evaluate the transfer of viruses or nutrients for example. Also
467 called the surface area product (PxS), it can be characterized by the influx volume transfer
468 constant K_{trans} (min^{-1}), equal to the product of the transfer constant and the blood volume
469 [80]. Several models to assess permeability have been developed, some neglecting the tissue
470 blood volume [81, 48, 59], other taking it into account (the extended Kety or Tofts General
471 Kinetic Model (GKM) [82]. Other models are able to assess both perfusion and permeability
472 [80, 83]. To our knowledge, only one study reported results about placental permeability,
473 which were obtained with a dual-echo MR imaging sequence [67]. However, this type of
474 analysis requires a high volume of injected contrast agent [62]. We are particularly
475 interested in assessing placental perfusion and not placental permeability in placental
476 insufficiency. Thus, contrast agents remaining only in the maternal intervillous space would
477 provide significant clinical information with safety.

478

479

480 **Human application**

481

482 MR Imaging of placenta accrete spectrum disorders (PAS) [84-101]

483 Previous studies using DCE-MRI in humans have focused on the assessment of PAS, without
484 describing quantitative parameters of perfusion [84-87]. Millischer et al [84] demonstrated
485 that a Gadolinium injection improves the ability of radiologists with the diagnosis of placenta
486 accreta with MRI. Liposomal-Gadolinium also appears to be of great interest, enabling
487 adequate visualization of the retroplacental clear space [36]. Romeo has shown, however,
488 that the simple use of non-contrast MRI, combined with ultrasound assessment of placental
489 adhesion spectrum (PAS), increased its probability of detection from 80 to 91% [88]. A recent
490 systematic review by Kappor [89] classifies MRI signs of PAS and highlights best practice
491 guidelines for imaging diagnosis of PAS. This will be covered in a separate article dedicated
492 to placental anatomy in this special issue.

493

494 MR Imaging of human placental perfusion

495 To our knowledge, only one study has demonstrated that the evaluation of human placental
496 perfusion by DCE-MRI is feasible. The Placentimage trial [102] evaluated in vivo placental
497 perfusion parameters in pregnant women undergoing termination of pregnancy between 16
498 and 34-weeks gestational age (GA). The mean value of the placental blood flow (FT) was 137
499 mL/min/100mL, concordant with the results obtained in human pregnancies by isotope
500 techniques [103] (110 mL/min/100 mL) and by echo planar imaging sequences (EPI) [104]
501 (176 + 24 mL/min/100 mL). FT decreased with gestational age, halving between the
502 beginning of the 2nd trimester and the end of the 3rd trimester, related to the growth of the
503 placenta, villous maturation, and to decreased placental efficiency over gestation (p=0.011).
504 The results also suggested that the FT and Ftotal values estimated by DCE-MRI in human
505 pregnancies could detect placental dysfunction with a tendency towards decreased values in
506 IUGR compared to non-IUGR fetuses (p=0.07 and p=0.0008, respectively). This work also
507 explored in vivo fractional blood volume, finding Vb values of 61.77%. These results should
508 be considered exploratory due to potential confounders such as different MRI sequences
509 and platforms, technical limitations, image failures, and limited reproducibility between
510 centers. However, this is the first study that has measured in vivo placental perfusion values
511 in pregnant women using Gd based contrast agents.

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513 Futures considerations

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515 This review shows the extraordinary range of data that the DCE can provide on the placental
516 function. It is the only technique capable of determining parameters of microcirculation
517 other than perfusion for example, permeability [67]. The data provided are quantitative, at
518 the cost of a certain complexity in the analysis of the data that are yet to be clarified. Finally,
519 it is the oldest and most robust technique (first publications in the 90s) and the most widely
520 used, mainly in the field of tumors [105-111]. In this, DCE-MRI is the functional magnetic
521 resonance imaging (f-MRI) technique unanimously recognized as the gold standard in the
522 evaluation of organ perfusion [12, 61, 62, 112, 113] and we demonstrate that, despite
523 current limitation related to uncertainty about contrast agent safety in human pregnancies,
524 as a technique it is also relevant for studying placental function.

525 Other functional MRI techniques may also be able to assess placental function, but not as
526 accurately and extensively as DCE-MRI could allow. ASL-MRI (Arterial Spin Labeling), uses
527 MRI pulses to magnetically label blood as an endogenous contrast agent [114]. Studies have
528 shown its feasibility for the quantification of placental perfusion in rats [115] and humans
529 [116-117]. Although its main strength is the absence of contrast agent injected, ASL-MRI is
530 nonetheless limited by the poor signal to noise ratio and its high sensitivity to motion
531 artifacts [61, 118]. Often criticized for its low SNR, Hartevelde nevertheless emphasizes that a
532 high SNR can be obtained on the condition of using low cutoff velocity (1.6cm/s) [119]. Other
533 non-contrast techniques, DWI (diffusion weighted imaging) and IVIM (intravoxel incoherent
534 Motion) are techniques that also makes it possible to assess perfusion parameters: ADC
535 (apparent diffusion coefficient) and perfusion fraction (f, %) by studying the movement and
536 diffusion of water molecules within tissues [120]. The exact nature of what is measured with
537 placental IVIM remains controversial [62]. Derwig et al have compared IVIM and ASL in the
538 assessment of placental perfusion in the second trimester in normal and fetal growth
539 restriction pregnancies and suggest that the FAIR-ASL sequence may offer a more practically
540 suitable method for routine clinical application than IVIM [121].

541 The future of DCE-MRI undoubtedly lies in the widespread availability of safe contrast
542 agents, be they Gd based or other. They make it possible to overcome several limitations of
543 the DCE-MRI which have hindered its development until now. Animal studies have shown
544 that some newer agents do not cross the placenta, suggesting that they might be safe if they
545 cannot reach the fetus. However, studies in humans are still lacking at present on this
546 subject. Remaining in the intervillous space, they make it possible to overcome the

547 complexity of compartmental analysis while retaining the potential to study the maternal
548 portion - the inter-villous space of the placenta, involved in the pathophysiological process
549 of placental insufficiency.

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557 **Conclusion**

558 DCE-MRI is the oldest and most robust method for assessing organ function as a
559 whole (perfusion and permeability). This depth and breadth make it to this day as a gold-
560 standard technique in studying perfusion. While its use in the human placenta has been
561 hampered by the need for gadolinium based-contrast agents whose safety remains
562 controversial, the recent development of novel contrast agents such as liposomal-
563 gadolinium and SPIO, two contrast agents that do not cross the placenta barrier, now
564 introduce new avenues for further exploration. In addition, with the increasing development
565 of other f-MRI techniques, exciting perspectives can be envisaged such as their combination
566 with each other, or wider application of such techniques in fetal interventions such as in
567 monochorionic twin pregnancies.

568 **Funding:** This research did not receive any specific grant from funding agencies in the public,
569 commercial, or not-for-profit sectors.

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Figure Legends

Figure 1: Example of dynamic contrast-enhanced magnetic resonance imaging of human placenta: A, After arrival of a bolus of intravenous injection of contrast media the aorta (red arrow) enhances; while the unenhanced placenta appears as low signal on T1-weighted sequences (blue outline). B-C, Shortly after the intravenous injection of gadolinium chelate in the arteries, the placenta enhances gradually and shows high signal on T1W images. After compartmental analysis of the enhancement, functional parameters can be evaluated.

Figure 2: The placental tissue enhancement curve

FT: Tissue blood flow, Vb: Tissue blood volume, PS: surface area product, Ve: Tissue interstitial volume.

Figure 3: Three-compartment model of the placenta. Exchanges of contrast media between the compartments are governed by transfer constants (k). q : quantity of contrast medium

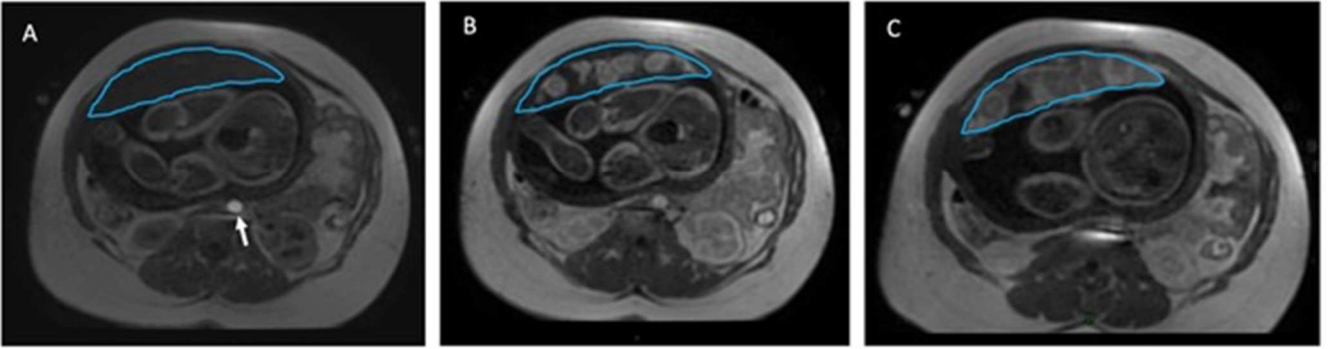


Figure 1

Figure 2

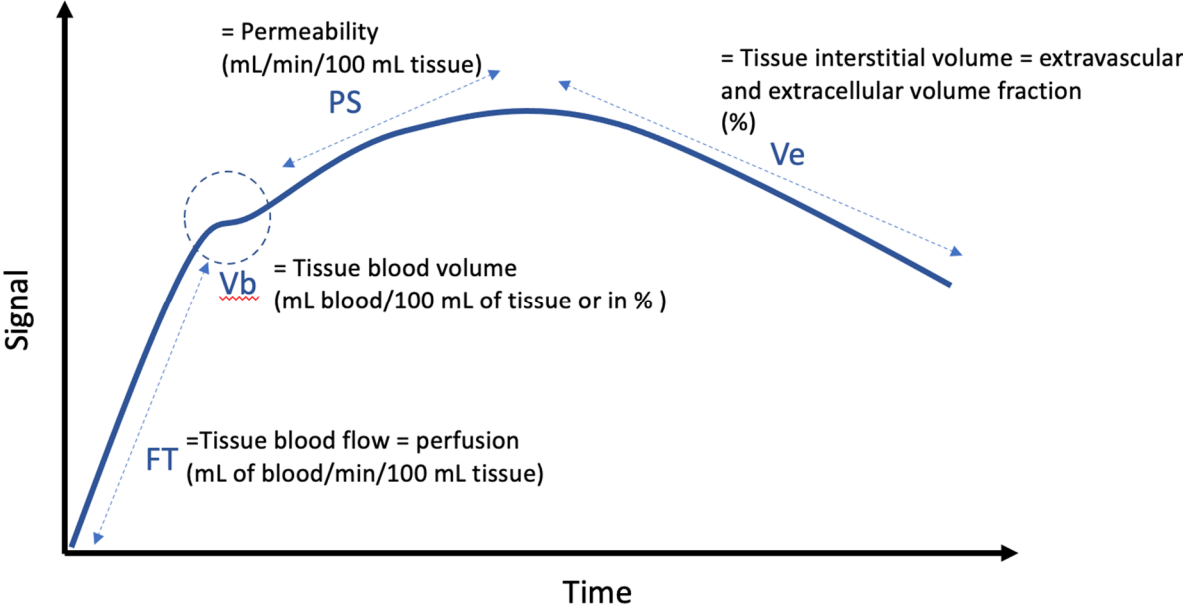


Figure 3

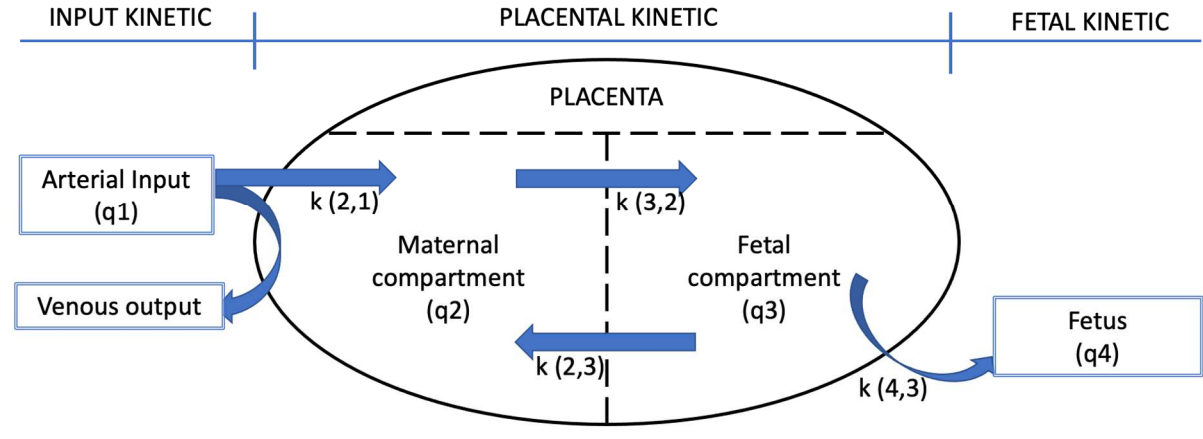


Table 1:

Title: Results of animal placental perfusion imaging studies in normal physiological conditions.

Caption: F: placental blood flow, Vb: fractional volume of the maternal vascular placental compartment, ED: embryonic day, Gd-CA: Gadolinium-based contrast agent, Gd: Gadolinium, T: Tesla, N/A: not applicable, 2D/3D: two/three-dimensional, HPZ: high perfusion zone, LPZ: low perfusion zone. NB: the length of pregnancy for mice is 19 days and 165 days for rhesus monkeys. All the EDs mentioned in the studies below therefore correspond to a period roughly similar to the third trimester in humans.

Table 2:

Title: Results of animal placental perfusion imaging studies in pathological conditions

Statistically significant results are denoted with an asterisk *

Table 3:

Title: Main characteristics of the three-compartment pharmacokinetic model compared to the steepest-slope model. AIF: Arterial Input Function

Table 4:

Title: Mains characteristics of Gd-CA, liposomal-Gd and SPIO contrast agents

ARTICLE	POPULATION	CONTRAST AGENT	IMAGING SEQUENCE	TYPE OF ANALYSIS	F (ML*MIN ⁻¹ *100ML ⁻¹) MEAN ± SD	VB (%)
SALOMON ET AL 2005[66]	36 mice (ED16)	Gd-CA	1.5T 2D fast spoiled gradient-echo sequence	Three compartmental model	128+60	N/A
TAILLIEU ET AL 2006 [67]	22 Mice (ED16)	Gd-CA	1.5T 2D fast spoiled gradient-echo single slice sequence with a dual echo time	Three compartmental model	180	36.5±0.9
REMUS ET AL 2013 [69]	5 mice (ED14.5) 5 mice (ED16.5)	Gd-CA	7 T 3D T1-weighted gradient-echo sequence	Steepest slope model	<u>Whole placenta</u> ED14.5: 135±29 ED16.5: 112±32 <u>HPZ:</u> ED14.5: 184±39 ED16.5: 158±58 <u>LPZ:</u> ED14.5: 119±28 ED16.5: 114±52	N/A
YADAV ET AL 2015 [70]	7 mice (ED13,15,17)	Gd-CA	7 T multi-slice 2D spoiled gradient echo sequence	Steepest slope model	<u>Whole placenta</u> ED13: 61,2±31,2 ED15: 90,26±43,67 ED17: 104,94±76,13 <u>HPZ:</u> ED13: 106±56 ED15: 139±55 ED17: 172±85 <u>LPZ:</u> ED13: 50±31 ED15: 73±39 ED17: 75±37	N/A
FRIAS ET AL 2014 [65]	1 rhesus monkey (G133)	Gd-CA	3 T T1-weighted 2D gradient echo sequence	Gamma Capillary Transit Time (GCTT) model	Volumetric flow rates: 25.26±10.3 mL/min	N/A
BADACHAPE ET AL 2019 [36]	24 FPU at E14.5, 20 FPU at E16.5, 23 FPU at E18.5 Mice	Liposoma I-Gd	1T T1-weighted 3D gradient-recalled echo sequence (T1w-GRE)	Steepest slope model	N/A	<u>E14.5:</u> 0.47 ± 0.06 <u>E16.5:</u> 0.5 ± 0.04 <u>E18.5:</u> 0.52 ± 0.04

Table 1

ARTICLE	CONDITIONS CONTRAST AGENT	POPULATION	IMAGING SEQUENCE	TYPE ANALYSIS	OF	F (ML*MIN ⁻¹ *1*100ML ⁻¹) MEAN ± SD	VB (%)
SALOMON ET AL 2005 [71]	Pharmacological model of preeclampsia Gd-CA	10 Noradrenaline mice 10 control mice (ED16)	1.5T 2D fast spoiled gradient echo monoslice sequence with double echo time	One-compartmental model		<u>Control group:</u> 72±84* <u>Noradrenaline group:</u> 126±54*	N/A
LEMERY ET AL 2018 [72]	Biological model of preeclampsia Gd-CA	18 L-NAME rats 12 control rats (ED16)	4.7T DCE- spoiled gradient echo	Single-compartmental model		<u>Control group:</u> Fetal layer: 301±188 Maternal layer: 124±95 <u>L-NAME group:</u> Fetal layer: 302±169 Maternal layer: 127±81	<u>Control group:</u> Fetal layer: 50±9* Maternal layer: 42±9* <u>L-NAME group:</u> Fetal layer: 56±13* Maternal layer: 49±13*
ALISON ET AL 2013 [68]	Surgical pathological model of IUGR Gd-CA	12 rats (ED19)	4.7T 2D spoiled gradient echo sequence (fast low-angle shot, FLASH)	Single-compartmental model		<u>Non-ligated horn:</u> Inner layer: 215±154* Outer layer: 117±76* <u>Ligated horn:</u> Inner layer: 116±57* Outer layer: 66±37*	<u>Non-ligated horn:</u> Inner layer: 41±12* Outer layer: 35±10* <u>Ligated horn:</u> Inner layer: 30±7* Outer layer: 26±7*
DROBYSHEVSKY ET AL 2015 [73]	Surgical ischemia model Gd-CA	Rabbit (ED25)	3T T1-weighted spoiled gradient echo sequence	Steepest slope model		<u>Baseline phase:</u> 77±7* <u>Reperfusion-reoxygenation phase:</u> 44±6*	N/A
ARTHUIS ET AL 2018 [75]	Surgical ischemia model Gd-CA	9 rats (ED19)	9.4T T1-weighted spoiled gradient echo sequence	Bi-compartmental model		<u>Non-ligated horn:</u> 90.9 mL/min/100 mL (IQR 85.1–95.7)* <u>Ligated horn:</u> 51.2 mL/min/100 mL (IQR 34.9–54.9)*	<u>Control group:</u> 18±5 <u>Ligated horn:</u> 12±4

REMUS ET AL 2018 [74]	Stress-acoustic model	20 mice (ED14.5.16.5)	7T Dual-echo 3D T1- weighted gradient-echo sequence	Steepest slope model	<u>Control</u> <u>HPZ:</u> ED14.5: 147±31* ED16.5: 141±29* <u>LPZ:</u> ED14.,5: 56±19* ED16.5: 83±20*	<u>Cases</u> <u>HPZ:</u> ED14.5: 123±21* ED16.5: 192±51* <u>LPZ:</u> ED14.5: 43±12* ED16.5: 107±31*	N/A
DELOISON ET AL 2012 [41]	Surgical pathological model of IUGR SPIO (Ferucarbotran)	32 rats	1.5T 2D fast spoiled gradient-echo multisection (FSPGR)	Single- compartmental model	<u>Non-ligated horn:</u> 159.4 ± 54.6*	<u>Ligated horn:</u> 108.1 ± 41*	<u>Non-ligated horn:</u> 39.2 ± 11.9% <u>Ligated horns:</u> 42.8 ± 16.7%

Table 2

	THREE-COMPARTMENT PHARMACOKINETIC MODEL	STEEPEST SLOPE MODEL
TYPE OF PERFUSION ANALYSIS	Quantitative	Quantitative
CHARACTERIZATION OF :		
- WASH-IN	- yes	- yes
- MICRO-CIRCULATION	- yes	- no
- WASH-OUT	- yes	- no
DISTINCTION BETWEEN HIGH AND LOW-FLOW COMPARTMENTS	difficult	easier
ADVANTAGES	- precise	- simple - numerical robustness (low standard deviation)
DRAWBACKS	- complex - high standard deviation	- choice of AIF - underestimation of 33% of the perfusion
STUDIES	[66,67,68,71,72]	[63,69,70,73,74]

Table 3

	GD-CA (GADOTERATE-MEGLUMINE)	LIPOSOMAL-GD	SPIO FERUCARBOTRAN	FERUMOXYTOL
BASIC ELEMENT	Gadolinium	Gadolinium + liposomal nanoparticle	Iron oxide	
MOLECULE DIAMETER	1nm	100nm	60nm	30nm
MOLECULAR COMPOSITION	Free gadolinium chelate	Preparation procedure described by Ghaghada [19]	Iron oxide core + carboxydextran coat	Iron oxide core + carboxymethyl-dextran coat
RELAXOMETRIC PROPERTIES AT 1,5T, ,37°C IN WATER (L.MMOL⁻¹.SEC⁻¹-	R1=3.6 R2=4.3	Nanoparticle-based T1 relaxivity of 35000 with dual-Gd liposomal agents	R1= 20 R2= 185	R1=15 R2=85
ELIMINATION PLASMA HALF LIFE	1.6h	18-24h	rapid initial intravascular phase (half-life 3.9–5.8 minutes), and a second distribution phase of 3 hours	14h
EXCRETION	Renal	Elimination from blood by the reticulo-endothelial system. Clearance by the liver and spleen	Stored with the body's iron reserve and used in hemopoiesis. Coating with renal and faecal excretion	

Table 4