The use of functional placental magnetic resonance imaging for assessment of the placenta after prolonged preterm rupture of the membranes in vivo: A pilot study

Jana Hutter | Laurence Jackson | Alison Ho | Carla Avena Zampieri
Joseph V. Hajnal | Mudher Al-Adnani | Surabhi Nanda | Andrew H. Shennan
Rachel M. Tribe | Deena Gibbons | Mary A. Rutherford | Lisa Story

Abstract

Introduction: Preterm prelabor rupture of membranes (PPROM) complicates 3% of pregnancies in the UK. Where delivery does not occur spontaneously, expectant management until 37 weeks of gestation is advocated, unless signs of maternal infection develop. However, clinical presentation of maternal infection can be a late sign and injurious fetal inflammatory responses may already have been activated. There is therefore a need for more sensitive markers to aid optimal timing of interventions. At present there is no non-invasive test in clinical practice to assess for infection in the fetal compartment and definitive diagnosis of chorioamnionitis is by histological assessment of the placenta after delivery. This study presents comprehensive functional placental magnetic resonance imaging (MRI) quantification, already used in other organ systems, to assess for infection/inflammation, in women with and without PPROM aiming to explore its use as a biomarker for inflammation within the feto-placental compartment in vivo.

Material and methods: Placental MRI scans were performed in a cohort of 12 women (with one having two scans) with PPROM before 34 weeks of gestation (selected because of their high risk of infection), and in a control group of 87 women. Functional placental assessment was performed with magnetic resonance techniques sensitive to changes in the microstructure (diffusion) and tissue composition (relaxometry), with quantification performed both over the entire organ and in regions of interest between the basal and chorionic plate. Placental histology was analyzed after delivery where available.

Results: Normative evolution of functional magnetic resonance biomarkers over gestation was studied. Cases of inflammation, as assessed by histological presence of chorioamnionitis, and umbilical cord vasculitis with or without funisitis, were associated
Preterm birth (PTB) is defined as delivery before 37 weeks of gestation and occurs in up to 8% of pregnancies in the UK. It is associated with fetal morbidity and mortality both in the neonatal period and beyond, particularly at very preterm gestations and where placental inflammation (chorioamnionitis) is present. As a result, PTB also constitutes an important burden for public health. Approximately 40% of cases of PTB are associated with preterm prelabor rupture of the membranes (PPROM). PPROM before 37 weeks of gestation complicates 3% of all pregnancies in the UK. The median time between membrane rupture and delivery in these cases is 7 days but where delivery has not occurred expectant management is advocated in the absence of signs of maternal infection, to reduce the morbidity and mortality associated with preterm delivery before 37 weeks.

Infection is a significant complication of expectant management, and can often occur in the fetus in the absence of clinical signs in the mother. Neonatal morbidity, including sepsis, cystic periventricular leukomalacia, intraventricular hemorrhage, and later development of cerebral palsy, are significantly higher among pregnancies with PPROM complicated by infection as assessed by chorioamnionitis in the placenta after delivery. Chorioamnionitis is also known to alter the immune profile of the infant at birth. Up to 71% of cases with PPROM have histological evidence of chorioamnionitis on placental analysis, particularly at early gestations, yet 30% can be subclinical, without signs of maternal fever, fetal tachycardia, uterine tenderness or purulent discharge. Expectant management may therefore increase risks for both mother and baby if signs of infection are not overt.

Placental histopathological assessment only allows a retrospective diagnosis of chorioamnionitis and does not facilitate timely antenatal intervention such as administration of corticosteroids and/or early delivery or in utero transfer. Advanced functional magnetic resonance imaging (MRI) techniques provide a means of quantifying tissue changes and have been used in the gastrointestinal tract and heart to discriminate between acute and chronic phases of inflammation in vivo. Placental MRI has been pioneered in normal pregnancies during hyperoxygenation and normoxgenation in the assessment of conditions including fetal growth restriction and preeclampsia revealing distinct phenotypes. Techniques include magnetic resonance relaxometry, targeting the paramagnetic properties of deoxygenated hemoglobin to gain insights into the oxygen concentration, diffusion MRI to identify microstructural changes to the villous trees and flow in the inter-villous spaces, as well as combinations of approaches leading to more distinct descriptions of placental compartmental properties.

This study aimed to assess the feasibility of MRI as a non-invasive antenatal assessment tool for evaluating intrauterine infection based on placental assessment. This could prove invaluable information for both the timing of delivery, and antenatal interventions, with the ultimate aim to minimize the morbidity/mortality associated with infection/inflammation in the context of PTB.

**MATERIAL AND METHODS**

**2.1 | Cohorts and clinical data collection**

Women with PPROM before 34 weeks of gestation were recruited prospectively from a tertiary referral hospital in South London (Table 1).
Preterm prelabor rupture of membranes was confirmed on clinical grounds using speculum examination and biochemically using the rupture of membrane (ROM) test (ROM Plus® Rupture of Membranes Test; Clinical Innovations) when consented. Inclusion criteria included 16–34 weeks of gestation, singleton pregnancy, not in active labor, and ability to give informed consent. Exclusion criteria were: diagnosis of gestational diabetes, preeclampsia, chromosomal abnormalities, any other diagnosis associated with placental insufficiency, maternal body mass index greater than 35 kg/m², multiple pregnancies, metallic implants, and claustrophobia. Following assessment of eligibility, written consent was obtained and an MRI scan was performed on a 3T MRI system (Phillips Best).

One participant, scanned because of suspected PPROM, did not have a confirmed ROM test, had normal amniotic fluid at subsequent scans throughout and did not continue to leak fluid vaginally, so the decision was made to exclude her from any subsequent analysis.

A control cohort was selected from existing data sets from three studies (19-SS-0032, 19/LO/0852, and 14/LO/1169) where women had been scanned between 16 and 39 weeks of gestation and delivery had occurred after 37 weeks of gestation, with a neonatal birthweight above the third centile. There was no evidence of hypertensive disorders in pregnancy in this control cohort.

The number of days from MRI scan to delivery (see Figure 1A for a timeline), pregnancy outcome including gestation, weight at birth, fetal sex, Apgar scores at 5 minutes, and postnatal and maternal complications were recorded. Placentae were analyzed histopathologically using a structured assessment and assessed both macroscopically and microscopically. Evidence for chorioamnionitis, umbilical cord vasculitis, funisitis, chorionic plate fetal vessel vasculitis, presence of thrombi, villitis, infarction, fibrin deposition, and maturation of the villi was recorded wherever available (see Figure 1B for the locations).

### 2.2 | MRI assessment

Women were scanned in a clinical 3T scanner using a 32-channel cardiac coil in supine position with adequate cushioning and positioning. Regular verbal communication was maintained throughout the scan. The scan time was limited to 60 minutes in blocks of 30 minutes with a break offered in the middle. Continuous monitoring of oxygen saturations, heart rate and blood pressure (in 10-minute intervals) was undertaken. Optimization of all sequences was performed previously to keep the acoustic noise below 98 db(A). Following localizer and preparation scans, anatomical scans of the entire uterus were performed using two-dimensional TSE sequences in five orientations. A B0 map was acquired and manual shimming using an in-house tool was performed focusing on the placenta. Then, a two-dimensional multi-slice multi-echo gradient-echo echo planar imaging sequence with four echo times was acquired to allow T2* mapping with the following parameters:

**TABLE 1** Patient cohort overview

|                  | PPROM                  | Control                |
|------------------|------------------------|------------------------|
| GA scan (weeks)  | 27.58 ± 2.69 (24.15–33.00) | 29.93 ± 4.40 (21.71–38.29) |
| Maternal age (years) | 32.48 ± 0.63 (31.85–33.12) | 34.00 ± 3.70 (25.01–45.13) |
| GA delivery (weeks) | 31.46 ± 2.94 (28.14–37.71) | 39.96 ± 1.28 (36.86–42.43) |
| BW delivery (grams) | 1663.75 ± 533.33 (1050.00–2600.00) | 3393.37 ± 446.10 (2026.00–4400.00) |

Note: Only the second scan from the participant scanned twice was included in the statistics presented here. The numbers indicate mean ± SD.

Abbreviations: BW, birthweight; GA, gestational age; PPROM, preterm prelabor rupture of membranes.

**FIGURE 1** Schemata of (A) the timelines involved and (B) the localization of relevant inflammatory processes in the placenta. GA, gestational age; MRI, magnetic resonance imaging; ROM, rupture of the membranes.
2.3 | Data processing

All MRI data sets were assessed for overt fetal pathology. Placental data from all three considered functional modalities was manually segmented by two experienced placenta observers (authors JH, AH) keeping a conservative margin to the chorionic and basal plate to avoid inclusion of any non-placental maternal tissue or amniotic fluid. These segmentations included the entire placental parenchyma for the multi-echo gradient echo scan and the diffusion MRI.

Mono-exponential decay models were fitted to the data acquired for T2* maps using an in-house python script to obtain proton density and T2* maps: 10 random initializations were performed and the voxel-wise median value was used. The diffusion data were processed in a similar way to a previous study to obtain maps of the apparent diffusion coefficient (ADC) and the fractional anisotropy (FA). Quantitative values were obtained as the mean over the entire placental parenchyma. Additional histogram-based evaluation was performed for the T2* values resulting in skewness and kurtosis values.

2.4 | Ethical approval

The data used for this study were acquired as part of three ethically approved studies reviewed by the relevant ethical committees:

**TABLE 2** Outcome for the PPROM cohort

| ID | Time ROM-MRI (weeks) | GA MRI (weeks) | GA delivery (weeks) | Time MRI-delivery (days) | T2* | Diff | Gender | Birthweight (centile) |
|----|----------------------|----------------|---------------------|--------------------------|-----|------|--------|----------------------|
| 1 (1) | 2 | 26.14 | 28.14 | 14 | x | Q- | Female | 82.9 |
| 2 (2) | 7 | 27 | 28.3 | 9 | x | x | Male | 79.6 |
| 3 (4) | 6 | 30.57 | 33 | 17 | x | x | Female | 34.6 |
| 4 (5) | 2 | 25.86 | 29.3 | 25 | x | x | Female | 88.6 |
| 5 (6) | 4 | 29.71 | 30.3 | 4 | x | x | Male | 5.9 |
| 6 (9) | 6 | 33 | 33.3 | 3 | x | Q- | Male | 83.8 |
| 7 (12) | 6 | 26.29 | 28.14 | 13 | x | x | Female | 57.7 |
| 8 (13) | 2 | 29 | 31.56 | 11 | x | x | Female | 61.6 |
| 9 (14) | 3 | 30 | 30.3 | 3 | x | x | Male | 68.6 |
| 10 (15) | 24 | 20.6 | 31.57 | 77 | x | x | Female | 37.4 |
| 11 (1502) | 53 | 24.7 | 31.57 | 106 | x | Q- | Female | 37.4 |
| 12 (225) | 7 | 19.42 | +(20.14) | +(5) | x | x | + | + |
| 13 (291) | 24 | 24.14 | 26.57 | 16 | x | x | MALE | 76.7 |

Note: ‘+’ signifies stillbirth before 23 weeks of gestation. Prolonged membrane rupture (ROM) times of more than 5 days are marked in yellow. Short intervals between MRI and delivery are marked in red (<5 days), yellow (5–25 days)*. Data sets with low quality that had to be excluded are marked with Q-.

Abbreviations: GA, gestational age; MRI, magnetic resonance imaging; ROM, rupture of membranes.

In total, 12 women with PPROM were successfully scanned (only the second scan from the one woman who underwent two scans has been included in the analysis). Eighty-seven control pregnancies were included for comparison. For the PPROM cohort, mean gestational age (GA) at MRI was 26+5 weeks (range 19–33 weeks), mean GA at delivery 29+2 weeks (range 20+1–33+3 weeks) with median duration from MRI to delivery 23+2 days (range 3–106 days). For the control cohort, median GA was 29+3 weeks. The pregnancy and birth outcomes for the PPROM cohort are given in Table 2.

Complete anatomical and relaxometry data were obtained and processed in all cases. Diffusion data were obtained in all cases, but judged of sufficient quality in only 10 cases. Histopathology results are given in Table 3 for the PPROM cases, illustrating some degree of maternal and/or fetal inflammatory response in all but one (corresponding to P10, P11). No signs of villitis, intervillitis, infarction, additional fibrin deposition, or accelerated maturation were observed in any of the control or PPROM cases. From the control cohort, 26 women had histological assessment, of which eight showed no sign of chorioamnionitis and 18 showed signs of chorioamnionitis at term.

Placental images from the 12 cases with PPROM, including the 10 scans with histopathological evidence of chorioamnionitis, are displayed graphically in Figure 2, with the later scan used for the
A woman who was scanned twice as outlined above. For each case, coronal and sagittal anatomical images through the placental parenchyma are given in the first row, together with a zoom into the cervix, to visualize length and degree of dilation. In the second row, T2*, ADC and FA maps are displayed for similar locations. The same scales are used for each functional category for all placentae.

### 3.1 Visual appearances

Anatomical changes were apparent in the sagittal displays for PPROM cases P1 and P5 with large areas of hypointensity close to the chorionic plate (marked with green arrows), that were not seen in control placentae. Smaller hyperintense areas were observable (pink arrows) in most cases but these were not present in the control cases of similar gestation.

Control T2* maps show an increasingly lobular appearance with more pronounced circular hyperintense areas surrounded by hypointense structures over gestation. These changes typically occurred homogeneously over the entire placenta. However, the T2* maps of the PPROM cases reveal pronounced, focal large areas of low signal—as indicated with green arrows in PPROM placentae P1, P2, P5, P6, P9, P12, and P13—which were not as visible in the anatomical images from the majority of women. P10 and P11, from the same woman, do not display these signs.

### 3.2 Quantification

Figure 3 illustrates for the control women a decrease in mean T2* over GA (controls slope −3.49, \( p < 0.005 \)), decrease in ADC over GA (Controls slope 0.55, \( p < 0.005 \)) and an increase in FA (Controls slow 0.62, \( p < 0.005 \)). Compared with these control values, the measurements from the PPROM placentae show decreased mean T2* across the GA range (PPROM cases slope −1.53, \( p = 0.295 \)), with a wider spread of values, although at a non-significant level. One notable exception, case P8, is marked by the black arrow. In addition, the ADC was not significantly reduced across GA from PPROM placentae (PPROM cases slope 0.42, \( p = 0.04 \)) and the FA values were increased (PPROM cases slope 0.63, \( p = 0.005 \)), compared with controls. Analysis of the progression over GA was performed to fit the known dependency of these quantities with GA.

The evaluation of these quantitative measures against histopathologically shown chorioamnionitis including the entire control

| ID  | Maternal inflammatory indicators | Fetal inflammatory indicators |
|-----|---------------------------------|------------------------------|
| P1  | Severe acute chorioamnionitis   | Umbilical cord vasculitis (vein) |
| P2  | Acute chorioamnionitis          | Umbilical vasculitis (3/3 vessels), neutrophils extending into Wharton’s jelly (funisitis), inflammation in the chorionic plate, occlusion of large central chorionic vessel, downstream focus of ischemic villi |
| P3  | Acute chorioamnionitis          | Acute chorionic vasculitis, acute umbilical cord vasculitis (1/3 vessels, acute funisitis) |
| P4  | No chorioamnionitis             | No histology                 |
| P5  | Acute chorioamnionitis          | Funisitis and chorionic vasculitis, two large non-occlusive thrombi in fetal stem villi |
| P6  | Acute chorioamnionitis          | Funisitis                     |
| P7  | Acute chorioamnionitis          | Funisitis and vasculitis      |
| P8  | Acute chorioamnionitis          | Pan-vasculitis, chorionic plate is acutely inflamed |
| P9  | Acute chorioamnionitis          | Acute chorionic vasculitis, acute vasculitis (3/3 vessels), acute funisitis |
| P10 | No chorioamnionitis             | No histology and no vasculitis, Occasional intravillous hemorrhages |
| P11 | No chorioamnionitis             | No histology                 |
| P12 | No histology                    | No histology                 |
| P13 | No histology                    | No histology                 |

Note: Colors emphasize normal finding (green), early stage of abnormality (orange), advanced, and very advanced stages (red and dark red). There were no signs of infarction, increased perivillous fibrin deposition, or evidence for decidual vasculopathy and all placentae showed normal maturation.

Table 3 Histopathological evaluation for the participants
cohort (Figure 4) did not reveal any clear correlation. However, the time between the MRI and the observed evidence for chorioamnionitis did vary largely, as is indicated by the transparency level in Figure 4—hampering our ability to draw conclusions.

4 | DISCUSSION

This study demonstrates, as far as we are aware, the first exploration of functional placental assessment in a cohort of women with PPROM compared with control women who delivered at term with uncomplicated pregnancies. We have demonstrated that multimodal functional MRI data can successfully be obtained from women with PPROM. Trends for normal controls were reaffirmed: ADC and mean T2* values decreasing and FA values increasing linearly with gestation. There were both qualitative and quantitative changes in PPROM cases, with an increase in FA values, no decrease in ADC, and a trend towards a reduction in T2* values.

There are several recent studies using MRI to study PTB, but these have focused on volumetric assessment of fetal organs. They found a reduction in lung volume and changes in the size of the thymus gland—known to play an integral role in the development of the fetal immune system and suggested as a marker of the fetal inflammatory response. Previous efforts to assess the placenta specifically detected changes of a bank-like T2-weighted hypointense signal and diffusion-weighted hyperintense signal changes associated with a diagnosis of chorioamnionitis in three of six patients. This current study goes beyond anatomical assessment and includes functional MRI properties of the placenta, which could complement fetal findings.

FIGURE 2 Imaging results of all preterm prelabor rupture of membranes (PPROM) cases P1–P13. P10 was omitted and the second scan of this woman, P11, was included. For each case, the anatomical images are displayed in the first row, coronal placental view, sagittal placental view and sagittal cervix view. The second row gives the functional T2* data in coronal and sagittal view matched to the anatomical data. Pink arrows identify regions of hyperintense small dots. Green arrows identify areas of reduced T2*. In the right column three exemplary controls are shown at similar gestational age.
The use of T2 and T2* relaxometry as a means of discriminating between acute and chronic phases of inflammation has previously been proposed in other organs such as the heart and the kidney and diffusion MRI has been used in the evaluation of inflammatory conditions of the gastrointestinal tract such as Crohn’s disease.14 However, no studies to date have evaluated whether these techniques can be used successfully to assess placental inflammation and hence may be indicative of chorioamnionitis in utero.

The quantitative values found in the control cohort are in accordance with literature values at 3T, showing decreasing T2* from approximately 100 to 20 ms and ADC and FA values between 0.002 and 0.003 mm²/ms and 0.3–0.9 (arbitrary units) from 10 to 40 weeks, respectively.17,19 Analysis of the PPROM cases revealed a number of changes in the placental parenchyma both visually and numerically reduced T2* values and markedly increased FA (p = 0.005). The observed heterogeneity in T2* values within the PPROM cohort reflects the complicated and highly dynamic physiological changes associated with ascending infection and the variability between time of imaging and subsequent delivery.

The quantitative changes observed in the placentae of PPROM pregnancies demonstrate a similar phenotype to women with pre-eclampsia who present with a reduction in placental T2* and ADC values and an increase in FA,19 although changes in PPROM are not as marked, when compared with the control group, and appear to be more localized. This potentially points towards a less extreme and more acute placental change in the PPROM cohort. It should be noted that none of the women with PPROM, nor any of the control cases, had hypertensive disorders of pregnancy or other diagnoses typically associated with placental insufficiency. The focus of this study is on PPROM pregnancies and associated phenotypes; however, the study design does not allow us to differentiate at this stage between placental insufficiency and inflammatory responses.

Increased FA values, evident in most PPROM cases, combined with decreased ADC in three cases may be indicative of microstructural changes within the placenta. Increased presence of neutrophils in the corresponding tissue could decrease diffusivity (reduced ADC value), and increased anisotropy (increased FA value) could reflect localized infiltration in the chorion. The
observed reduced T2⁺ could be linked to reduced transport of oxygenated hemoglobin as a downstream effect of the inflammation. However, the cited changes in structure, the changed water content as well as any other changed tissue property might influence the transverse relaxation rates.

The cases of PPROM with the longest period since ROM and the shortest time interval to delivery (cases P5, P6, and P9) displayed the clearest phenotype, which is in line with the inflammation being the most acute in these cases. Other cases such as P4, P12, P7, P10, and P11 displayed minimal changes compared with control women. The normal histopathological evaluation in P10, P11 might indicate no sign of inflammation which corresponds to this result. This observed variation on MRI is likely to reflect several factors involved in PTB, such as inflammation, cervical changes among other, and severity of chorioamnionitis, which initially affects the maternal compartment before progressing to the fetal tissues, resulting in differing characteristics on placental histology.²⁹-³¹

The maternal inflammatory response is characterized first by microbial invasion of the chorion, amnion, and chorionic plate before progression to epithelial necrosis of the amnion.²³,²⁹ Where this process is localized to a specific area of the placenta (such as for case P2) mean T2⁺ is not as low as in cases where the invasion is more diffuse (cases P1 and P5 for example). In addition to the chorionic plate, more advanced disease may also affect the amnion combined with vasculitis of the chorionic vessels. Further disease progression results in the fetal inflammatory response, which is associated with poorer neonatal outcomes.³²

This is characterized by leukocyte infiltration of the umbilical cord vessel wall or Wharton's jelly. Such changes are, however, harder to identify from the MRI results because of the small diameter of the vessels and the variability in location. However, the most significant fetal compartment infection is associated with the presence of thrombi within the villous tree.³² This may be reflected by the substantially reduced T2⁺ areas: the distribution of these is in accordance with placental lobules reflected by individual villous trees and the presence of a thrombus may result in tissue with a reduction in oxygen content.

These findings may have clinical implications in the future to assess the extent of chorioamnionitis and stratify individual patients' risks accordingly. It would also be of interest to combine both fetal and placental MRI findings to grade disease process and duration.

The lack of a reference standard technique to assess for signs of inflammation in vivo, specifically at the time of MRI, hinders further evaluation. Although histopathological assessment of the placenta after delivery facilitates a definitive diagnosis, it is undertaken at a time-point remote from the MRI. In this study, the time between delivery and MRI varied between 2 and 27 days for the PPROM cases. Furthermore, the time between ROM and the scan also varied between 2 and 7 days, further limiting conclusions that can be drawn. The targeted patient cohort, women with PPROM, and the resulting unpredictable and short time window (delivery in 50% of cases within a week) and need for close clinical observation during the scan render this study highly challenging; however, they also make this data set unique. In future, expansion of the study will allow grouping along similar timings and hence more insight into the dynamics of the observed challenges.

Given the course of the ascending infection traversing each layer from decidua to chorion to amnion, a higher resolution and greater focal evaluation would add specificity to the assessment of the timing of the infection and inflammatory response. Further advances in MRI acquisition and reconstruction strategies would enable the use of further high resolution three-dimensional reconstruction techniques and so facilitate this in the future. Efforts to display the placental tissues in an agreed coordinated system could further add to the specificity of the localization of lesions.³⁴,³⁵

To usefully translate these results, following a larger observation study, would be a randomized control trial to assess whether altering the timing of delivery in PPROM in response to MRI biomarkers of infection/inflammation could result in a reduction in neonatal morbidity and mortality. Combined analysis with biomarker-based serum scores might further enable the development of individual risk scores.³⁶,³⁷ Phenotyping different presentations in more detail together with histopathological assessment will allow additional insights into the cascade of events starting from the ascending infection through the layers of the placenta to widespread fetal infection.

5 | CONCLUSION

Functional placental MRI reveals a range of placental changes, associated with inflammatory processes confirmed on subsequent histology. It shows promise as a tool to noninvasively identify inflammation in vivo, and could therefore assist in improving optimal timing for interventions designed to prevent fetal injury, such as antenatal corticosteroids and magnesium sulfate and the need for delivery and/or in utero transfers where indicated.

CONFLICT OF INTEREST

AHS is the chief investigator on a number of trials funded by NIHR and charity sources related to preterm birth prediction and prevention. Clinical Innovations provided the ROM Plus® Rupture of Membranes Tests for this study. Hologic Biomedical and Qiagen have provided samples for these studies. Hologic have provided funding (paid to the institution) to evaluate technical performance of their samples. There are no other conflicts of interest.

AUTHOR CONTRIBUTIONS

JH and LJ: data collection, writing, editing. AH: recruitment, data collection, writing, editing. CAZ: data collection. JH, MA- A, SN and AHS: data collection, funding, editing. RMT and DG: editing. MAR and LS: data collection, funding, editing.

ORCID

Jana Hutter https://orcid.org/0000-0003-3476-3500
Andrew H. Shennan https://orcid.org/0000-0001-5273-3132
Rachel M. Tribe https://orcid.org/0000-0003-3675-9978
Deena Gibbons https://orcid.org/0000-0002-7953-3576
Mary A. Rutherford https://orcid.org/0000-0003-3361-1337
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