Data sharing: using blockchain and decentralized data technologies to unlock the potential of artificial intelligence: What can assisted reproduction learn from other areas of medicine?

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The extension of blockchain use for nonfinancial domains has revealed opportunities to the health care sector that answer the need for efficient and effective data and information exchanges in a secure and transparent manner. Blockchain is relatively novel in health care and particularly for data analytics, although there are examples of improvements achieved. We provide a systematic review of blockchain uses within the health care industry, with a particular focus on the in vitro fertilization (IVF) field. Blockchain technology in the fertility sector, including data sharing collaborations compliant with ethical data handling within confines of international law, allows for large-scale prospective cohort studies to proceed at an international scale. Other opportunities include gamete donation and matching, consent sharing, and shared resources between different clinics. (Fertil Steril® 2020;114:927–33. ©2020 by American Society for Reproductive Medicine.)

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For the last three years, prediction algorithms using artificial intelligence (AI) tools have gained particular prominence at assisted reproductive technology (ART) conferences (1, 2) and in peer-reviewed publications (1). The objective is to improve the efficacy, efficiency, and consistency of clinical decisions made during an ART treatment, such as embryo classification and selection, sperm identification and classification, and clinical decisions during stimulation (3, 4). However, tools based on AI require large amounts of data to learn the association between a range of factors (input data) and predicted outcome (output data) (2). Up to now, this dependency on data volume, quality, and diversity has restricted the progress of AI tools toward becoming sufficiently robust for safe clinical implementation. In addition, interclinic variation in data point definitions, patient demographics, and differences in clinical and laboratory practices may cause data bias, resulting in AI tools that cannot be generalized because they are based on training in one original clinic (5).

With the limitations in mind, one way to overcome data insufficiency and data bias would be access to

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archives of large, global, and diverse data (6), representative of different patient demographics and clinical settings (7). With more than 2.7 million ART cycles per year worldwide (8), this goal should be theoretically easily achievable because sufficient varied data exist. The challenge lies with collecting, handling, amalgamating, and accessing the necessary data.

First, health care data are highly sensitive, requiring strict regulation and adherence to standards with regard to preservation of the privacy and confidentiality of the patients, traceability and transparency of all interactions with the data, accountability of the data controller and the data processor, security of access to the data, and other ethics considerations (9). The consequence has been a convoluted process from the time the data are collected to the time research can start, which includes consenting of participants, data organization and processing, regulatory approval, ethics approval, and local clinic approval. This process usually takes months if not years to complete, and it not only extends the time and the cost of learning from and applying clinical data to improve clinical practice but also limits exploratory research on multicenter data to answer very specific study questions. Streamlining this process in a manner that preserves the standards of research would therefore help the field evolve faster, translating benefits directly to professionals and patients.

Second, the data from the 2.7 million cycles performed each year worldwide vary in definition and standards of validation with regards to accuracy and completeness. Moreover, most in vitro fertilization (IVF) clinics are still collecting data either wholly or in part in paper form. This highlights the need to enhance the digitization of IVF clinics and incorporate a culture of understanding the value of data integrity and to ensure that the various solutions employed to collect data are integrated with each other. Paper and inaccurate or disjointed data greatly reduce the potential of AI analytics tools.

Third, the IVF field lacks a system to amalgamate data effectively. At the global level, organizations such as the International Committee Monitoring Assisted Reproductive Technologies (ICMART) are only capable of collecting summary data, which is impossible to verify. At the national level, data sets such as that from the Human Fertilisation and Embryology Authority (HFEA) have obvious limitations. Indeed, they are set up for regulatory purposes not for research, so they lack the detail necessary to answer basic clinical practice questions. Not all countries have such mandatory registries, and an international version of the HFEA registry is not possible given the varying regulations among countries on how data move across international borders. As a result, it is very difficult for AI researchers to access sufficient good-quality data to use in training algorithms to make relevant predictions that could help clinicians make better decisions. In the process of handling sensitive health data, traceability and immutability should be prerequisites to track and monitor any interaction with that data.

A blockchain is an immutable ledger containing a time-stamped series of records of data that is managed by a distributed, decentralized cluster of computers. It records all events occurring in the network in a "chain of blocks" that cannot be altered once recorded. By making this ledger accessible to all members of the network, it allows trustless transactions. For public blockchains, anyone can be part of the network, and the blockchain is maintained by the public community. This is the case, for example, for Bitcoin, Ethereum, and Dash. For private blockchains, entrants need a permission to participate in the network, and the ledger of transactions is only accessible to validated participants.

Blockchain has been around since 2008 when the Bitcoin white paper was published, setting the groundwork for a distributed ledger technology that, at the time, focused on electronic financial transactions. Since then, new potential uses have been found for the technology. The second generation of blockchain allowed for smart contracts (10). The third generation has extended to nonfinancial applications of blockchain (e.g., insurance, supply chain, dispute resolution, identity management, and health care). The novelty lies in the application of blockchain-based technologies in health care as a tool to address sensitive data-sharing challenges (11). We provide a systematic review of blockchain uses within the human health care industry, and blockchain's relevance to the IVF field.

METHODS AND DESIGN

This review was done using the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) guidelines to search four different scientific databases (PubMed, IEEE Xplore, Web of Science, and Scopus) with the search string "blockchain" AND ("health*" OR "medic*" OR "biomedic*" OR "clinic*" OR "fertility*" OR "IVF*"). Relevant publications were selected and analyzed. The search was performed on January 26, 2020.

Inclusion criteria

The review includes peer-reviewed publications with a major focus related to the application of blockchain in health care, papers written in English. Only journals with a selective editorial policy and tracked by Clarivate, Scopus, or SciELO were considered.

Exclusion criteria

We excluded studies that were performed with nonhuman species. We also excluded studies published in languages other than English and reviews.

Study selection

After the duplicates were removed, two investigators independently assessed the titles and abstracts of all the articles. Studies that did not meet the inclusion criteria were excluded. After this first step, the text of the selected studies was evaluated fully. Disagreements regarding inclusion were resolved by consensus or with the involvement of a third author.

The search across all databases did not reveal any blockchain proposed for the purpose of IVF/fertility. As a systematic literature review from academic search engines, this study did not include blockchain technologies advertised on the Internet or elsewhere, as this was considered outside the scope of this study. Additionally, the use of English terms in the search engine excludes publications in foreign languages.

RESULTS

The review revealed 55 studies proposing various blockchain models with different use cases in health care (Fig. 1; Supplemental Table 1, available online) (12–67). Technologies that enable AI only represented a minority of the studies among those using blockchain in health care.

Most blockchain publications (69%, 38 papers) were in the area of general health, followed by clinical trials/biomedical research. There were also examples in diabetes, oncology, chronic disease, insomnia, dentistry, genomics, and pain management. The search across all databases did not reveal any blockchain proposed for the purpose of IVF/fertility. The number of publications increased from four publications in 2016 to 26 publications in 2018, and have since decreased to 10 in 2019 (Supplemental Table 2, available online). Of these proposed blockchains, 84% did not involve federated learning and 16% did (Supplemental Table 2). Over quarter of these proposed blockchains were developed in the People's Republic of China (30%), and 20% by the United States, and others were by collaborations across countries (Fig. 2). Over half the publications used were proposed for electronic medical records (56%) and remote patient monitoring (13%); 5% were designed for drug/pharmaceutic supply chain, 9% for biomedical research/education, and 11% for health data analytics (Table 1).

DISCUSSION

This systematic literature review demonstrates that blockchain-based technology has been used in many health care fields (predominantly general health), with the overall number of publications increasing over time. Most publications involve academic projects rather than industry, with the People's Republic of China and the United States leading in terms of the number of publications.

Most studies focused on facilitating data-sharing between clinics in a decentralized way and among research institutions to enhance evidence-based medicine and improve standards of care. A marginal number of studies focused on data analytics applications despite the importance of the use case. One specific use of private blockchain technology can be to orchestrate in a secure and traceable way the access to decentralized sensitive data by predictive algorithms and, as such, enable AI studies in health care.

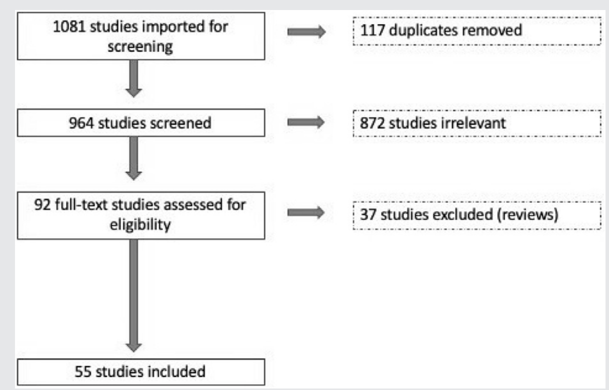
In this application, the first step of a blockchain involves a "data requester" such as a researcher or a data scientist requesting access for the algorithm to access data from the "data provider," such as a clinic or a hospital. Using blockchain in this application, this transaction request is recorded as a block of information in an immutable ledger. The network then verifies and manages the transaction through a cluster of computers, ensuring security standards are met and creating another block. A permission system ensures the access is permitted, creating another block. The chain of immutable blocks allows for monitoring the circulation of models and algorithms from one data provider to the other and provides reliable traceability of such transfers. It also provides the proof that different members execute the transactions they committed to doing, and makes them accountable for their actions. The process can then generalize to a large number of data providers and data requesters for unlimited progress (Fig. 3).

In the context of data analytics, federated learning is a learning paradigm that seeks to address the problem of data governance and privacy. It enables the efficient training of machine learning algorithms on various decentralized data sets without the need for exchanging the underlying data sets (7). The main advantage of this solution is that it allows learning from data located in different sources without the need of centralizing the data, as in traditional machine learning tasks.

Federated learning technology on its own solves the problem of efficient learning from decentralized data sets but does not respond to the security requirements of sensitive data access and processing within hospitals. Blockchain technology combined with federated learning as the baseline for a democratized data-sharing platform may be the technology to resolve the existing challenges in data sharing in ART, providing a potential solution for accountable and secure data sharing to allow collaborations that are compliant with ethical data handling within the confines of international law. This would allow trustless collaboration between data providers and data processors to enable powerful data analytics from multicenter, sensitive data and unlock the potential of AI. The use of blockchain-based technologies would certainly be more responsible and compliant with the required high standards of health care data-handling than the currently used paper-based or unsecure and/or inefficient digital data methods.

The fact that no publications were found in academic journals for the use of blockchain for data sharing in ART does not mean that blockchain is not currently used in ART. We have recently joined the Healthchain and the Apricity Data Hub collaborative data-sharing projects, confirming

FIGURE 1



Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flowchart.

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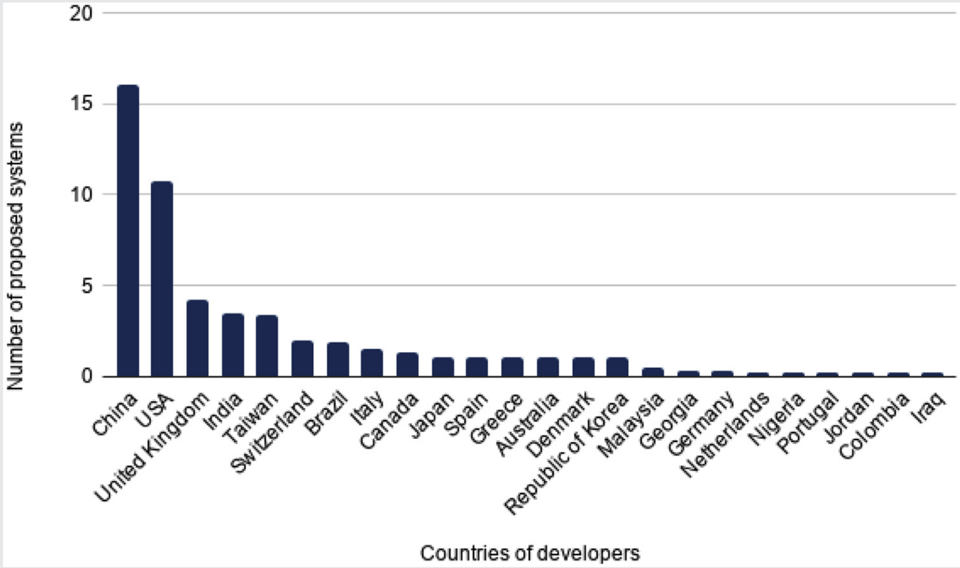
FIGURE 2



Countries associated with blockchains.

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that blockchain has found its way into the ART field. We also are aware of other potential commercial uses of blockchain in ART, including facilitating gamete and embryo donation matching, and gamete and embryo donation to research; traceability of data during cryotransport and cryostorage in centralized biorepositories; and sharing resources between clinics and consent sharing between research and clinical institutions. In particular, signing consents would be a textbook use case for blockchain in IVF. Signed consents along with timestamps can be added to the blockchain. Because the chain is immutable, it is impossible to unsign or change the time stamp after the fact. Blockchain would also be useful as an immutable ledger for arrival, departure, and expiry records in tracking clinic supplies, enhancing transparency in the supply of equipment and consumables, including drugs.

Scalability, speed, interoperability, security, and patient engagement are among the challenges of blockchain-based technologies reported in some of the publications listed earlier. Although some of these challenges have been resolved with the most recent blockchain applications, these challenges are best mitigated using ART-specific standards that do not currently exist. A multidisciplinary consensus group met during the European Society of Human Reproduction and Embryology (ESHRE) 2020 conference, and the publication of standards specific for data-sharing for academic reasons is expected to be published in 2020. Strategically, these standards should ensure that if different blockchain applications are set up by different vendors, they are capable of integrating with each other thanks to interoperation with a single source of truth. For now, without a standardization it

TABLE 1

Use cases of blockchain in health care and examples of proposed systems.

Use case	No. of proposed systems	Percentage	Examples of proposed systems
Electronic medical records	31	56	DPS (14), DAPPS (15), MedBlock (23), MedRec (24), MeDShare (25), Ancile (42)
Pharmaceutical supply chain	3	5	Modum.io (17), Gcoin (21, 63)
Health data analytics	6	11	19, 54, ModelChain (66, 67)
Health insurance	1	2	MIStore (26)
Prevention	2	4	
Remote patient monitoring	7	13	BMPLS (32, 33), Logitboost (34), HealthSene (40, 41, 49)
Biomedical research and clinical trials	5	9	45, 46, 54, 60, 66

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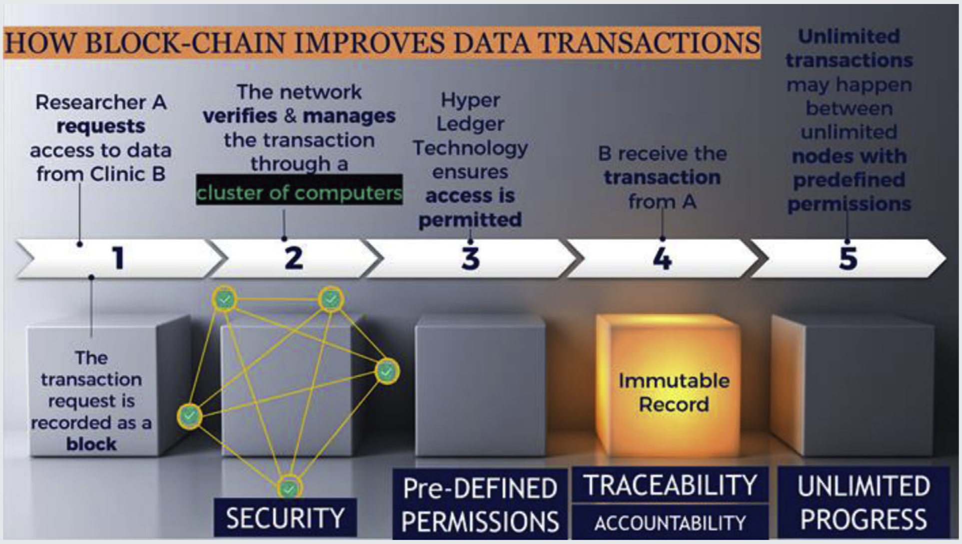
FIGURE 3



How blockchain improves data transactions.

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would be very difficult to integrate different blockchains created for different purposes.

With regards to security protecting privacy, there is a need to ensure that [1] the identity of a patient in a blockchain is not revealed, especially when combined together with data from other sources, which is a particular risk for patients who have rare conditions; and [2] the encryption cannot be breached by intentional malicious attacks, as has been reported with exchange platforms associated with cryptocurrency blockchains. The private keys used for data encryption require special attention with regards to restricted access. Compliance needs to be kept up to date with the continuously evolving regulations on health care data protection (such as the EU General Data Protection Regulation, the "right to be forgotten," and the U.K. Human Fertilisation and Embryology Act of 2008). Security threats can be mitigated with rigorous software development processes and permissioned protocols.

Regarding scalability, the high volume of data in ART, with increasing image- and video-based data, means that special attention needs to be paid to speed and scalability of the blockchain platform to prevent performance degradation and latency. For instance, platforms should avoid all the nodes in a platform to validate a process (12). All these challenges can be overcome with blockchain smart contracts (10), which outline defined rules to frame how the health care data are handled. Such rules may themselves introduce bias. Engaging patients during the consenting process is another challenge that could introduce bias. For instance, older patients may be less likely to engage than younger patients (13).

Local protection laws are strengthening all over the world. In many countries, it is now forbidden for ART patient data to leave the country, even when it is pseudonymized, which restricts international studies from emerging. This is preventing progress in the ART field, especially with regards to AI. A decentralized data structure secured with blockchain-based technology would keep the data in the clinic, under the control of the data controller (i.e., the clinic responsible for the data) with only algorithms moving between clinics. The algorithms would only access a pseudonymized version of the data, preserving confidentiality of identifiable information. The movement of algorithms across international borders is compliant with current international regulations. Therefore, blockchain-based technologies allow us to have our cake and eat it, too: we do not have to compromise between protecting the patient's privacy and evolving as a field based on large-scale collaborative data sharing. Such data-sharing technologies meet the legal, ethical, and information governance compliance standards.

Traditional multipartner cohort studies require a high level of trust between different centers. Trust can be achieved by a combination of reputation, human relationships, and/or strong contracts. Technology and, more specifically, blockchain applications have a great complementary role to play in enforcing trust for multipartner studies by framing what can and cannot be done with the data and the results of computations (i.e., AI predictive models).

Research "rules" are required for AI applications. Some guidance documents, while being relevant, are being updated to include AI (e.g., TRIPOD, CONSORT/SPIRIT). Similarly, journal referees may struggle if not well equipped with the nuances of being able to differentiate between a good and poor AI study. Another challenge in AI review is the reproducibility of experiments. With the traceability of events that occurred on the data with a blockchain-based technology, it may be easier to reproduce the results of an experiment.

Blockchain-based technologies for data sharing in ART promote collaborative research and innovation while reducing the cost of innovation validation and implementation. It is the natural progression for the ART field, in line with other areas of health care. Pattern recognition across different data sets can quickly help address the issue of reproducibility, which is often the downside to small single-site AI applications.

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